THE 1951 YEAR BOOK *of* MEDICINE

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Departments *of the* Year Book *of* Medicine

Infections

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PUBLISHER'S NOTE

The dates appearing under the title of this YEAR BOOK indicate that journals received within that period have been reviewed by the editors in selecting the articles abstracted herein

INFECTIONS



PAUL B BEESON MD

PART I

INFECTIONS

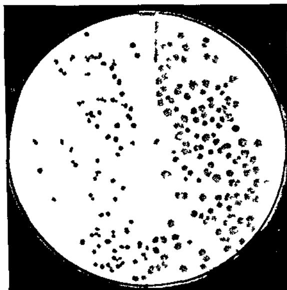
CHEMOTHERAPY OF INFECTION

Reactions of Bacteria to Chemotherapeutic Agents according to Lawrence P Garrod[1] (Univ of London) may be described as suppression habituation or acquired resistance dependence and stimulation It is interesting to speculate on events if the sulfonamides had remained the only agents for treating bacterial infections Almost all species can become resistant to these drugs and resistance to one drug involves resistance to all others The mechanism involved is the formation by the organism of a sulfonamide inhibitor shown in some cases to be p aminobenzoic acid The first organism observed to be resistant was the gonococcus The originally resistant strains naturally became increasingly prevalent and the proportion of treatment failures steadily increased Ample proof exists that clinically resistant disease is due to strains demonstrably drug resistant in vitro It is fortunate that the closely related meningococcus has behaved so differently Meningococcic meningitis is the only acute bacterial infection for which sulfonamides still are used in preference to penicillin Resistant strains of the two most important sulfonamide sensitive pecies pneumococcus and hemolytic streptococcus have appeared but have not been common

There is one strong point of resemblance between sulfonamide resistance and penicillin resistance the major difficulty occasioned by each is in infection by a single species the gonococcus and staphylococcus respectively Moreover in each instance selection and not adaptation is the mechanism by which resistant strains have become prevalent Resistance to penicillin in other species presents no such problem However it is commonly believed that widespread use of penicillin often in inadequate doses will eventually produce strains of bacteria other than staphylococci which are resistant to the drug Some

(1) B L M J 1 205 210 F b 3 1951

centers in which sulfadiazine prophylaxis led to the prevalence of resistant hemolytic streptococci scarlet fever and other in fections became more common in treated than in untreated men It was postulated that the drug was acting as a growth stimulant to these resistant streptococci If penicillin can stimulate bacterial growth it is more serious and there is evi dence that it can From the clinical viewpoint this evidence



F g 1—D d 1 g pl t cult f P pyocy cul ted f m 1 w k ld b oth cult t 37 C f 17 h M d m n gbt b lf onta 4 n t f p ll /ml ller colon 1 g d p gme t mo p 1 (C t y f G od L P B t M J 1 05 210 F b 3 1951)

rests largely on the occurrence of superinfections during penicillin therapy During local treatment of the mouth and throat the normal flora is largely replaced by resistant coli form bacilli The same thing can happen elsewhere with more serious results An account of 10 cases of Pseudomonas pyo cyanea *infection* is interesting Although penicillin was not suspected of being involved in producing or aggravating these infections seven patients six of whom died were treated with penicillin either shortly before or during the infection

Substitution of resistant for sensitive organisms is ex

organisms do become more resistant in the body during unsuccessful treatment

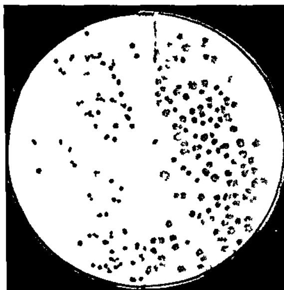
All species of bacteria can become highly resistant to streptomycin often rapidly not only in vitro but in vivo Since streptomycin resistance is permanent a time may be visualized when most of the sensitive bacteria will have acquired resistance The finding of resistant strains of Bacterium aerogenes and other coliform bacilli in the urine of patients with no history of having taken the drug is not uncommon This must mean that they are being disseminated from treated patients Whether because of this streptomycin should be reserved for treatment of tuberculosis to preserve its usefulness in this disease as long as possible is a matter of opinion Fortunately simultaneous administration of p amino salicylic acid appears to reduce greatly the frequency with which strains of tubercle bacilli become resistant

It was originally claimed that resistance to aureomycin and chloramphenicol does not develop It is oo early to decide how untrue this belief was Increases in resistance to aureomycin or chloramphenicol ranging up to about 50 fold in various species of gram negative bacilli have been reported either produced deliberately or occurring in treated patients Terramycin appears to behave similarly and it is interesting that organisms made resistant to it also become resistant to both aureomycin and chloramphenicol

The strange phenomenon of nutritional dependence on a substance normally lethal is another aspect of the peculiar behavior of streptomycin Organisms that fail to grow in absence of this drug can often be found among resistant organisms in infected urine It is theoretically possible that a patient infected with such organisms could be made worse by streptomycin treatment and improve on its cessation Similar dependence of certain bacteria on penicillin and chloramphenicol has also been demonstrated

The fourth type of bacterial reaction stimulation is less familiar There is good evidence that this effect is produced by concentrations lower than those required to inhibit growth If this is so it is only an illustration of the Arndt Schulz law which states that poisons are stimulants in small doses There is considerable evidence that this law applies to antibacterial chemotherapeutic agents In one of the U S Navy training

centers in which sulfadiazine prophylaxis led to the prevalence of resistant hemolytic streptococci scarlet fever and other infections became more common in treated than in untreated men It was postulated that the drug was acting as a growth stimulant to these resistant streptococci If penicillin can stimulate bacterial growth it is more serious and there is evidence that it can From the clinical viewpoint this evidence



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rests largely on the occurrence of superinfections during penicillin therapy During local treatment of the mouth and throat the normal flora is largely replaced by resistant coliform bacilli The same thing can happen elsewhere with more serious results An account of 10 cases of Pseudomonas pyocyanea infection is interesting Although penicillin was not suspected of being involved in producing or aggravating these infections seven patients six of whom died were treated with penicillin either shortly before or during the infection

Substitution of resistant for sensitive organisms is ex

plained by some authors by the theory that elimination of existing bacteria leaves a vacuum which is bound to be filled by others This theory certainly does not account for all cases because during penicillin treatment resistant bacteria may appear where there were no bacteria before Such an occurrence seems particularly likely in the urinary tract during excretion of penicillin given for disease elsewhere In three of the author s patients under treatment for bacterial endocarditis urinary infections due to Ps pyocyanea developed for no apparent reason other than presence of the drug in the urine

If penicillin stimulates or accelerates bacterial growth it should be possible to demonstrate this in vitro Recently Garrod studied acceleration of bacterial growth by penicillin by comparing the size of colonies on penicillin containing and normal mediums There was no doubt that such acceleration occurred (Fig 1)

Thus far the supply of new antibiotics has more than matched the capacity of bacteria to resist them but if this supply should cease and presumably the number yet to be discovered is limited the time may come when a few of the more enterprising species will flourish more or less unhindered

[A thought provoking and somewhat unsettling discussion One wonders what place penicillin aureomycin *et al* will have 10 years from now Certainly we are reaching a stage of diminishing returns in the search for new antibiotics of value A time may come when we find ourselves with less effective treatment for certain infections than at present —Ed]

Combined Action of Penicillin with Streptomycin or Chloromycetin® on Enterococci in Vitro A synergistic effect of penicillin streptomycin mixtures has been demonstrated both in vitro and in vivo With enterococci mixtures of penicillin and streptomycin in vitro rapidly cause death of the entire bacterial population whereas streptomycin alone has no effect and penicillin alone has mainly bacteriostatic properties Clinical reports indicate that combined therapy with the two drugs often cures bacterial endocarditis due to enterococci which ordinarily fails to respond to either drug alone E Jawetz J B Gunnison and V R Coleman (Univ of California) report experiments which add to the understanding of this antibiotic synergism During these studies it was also noted that chloramphenicol interfered with action of penicillin on

(2) Science 111 254 256 M 10 1950

many strains of enterococci in vitro It was therefore included in these experiments to compare streptomycin penicillin synergism with apparent chloramphenicol penicillin antagonism

Results were fairly uniform with all nine strains of enterococci studied With penicillin alone in optimal amounts for the particular organism the count of viable bacteria in the cultures decreased to low levels in 24-48 hours but after an additional 24-48 hours the population again increased to levels somewhat below those of the controls without drug Streptomycin alone completely failed to inhibit the large bacterial inoculums used When streptomycin was added to penicillin the rate of bactericidal action was greater than with penicillin alone The mixture of streptomycin and penicillin usually completely sterilized the medium The combined effect of streptomycin and penicillin on enterococci thus is evidently more than a summation of the individual drug effects and must be a true synergism of the two drugs

Chloramphenicol alone had no significant effect on the bacterial population However when mixed with penicillin the rate of bactericidal action was less than with penicillin alone The low number of viable bacteria attained with penicillin alone in 24 hours was not reached with the chloramphenicol penicillin mixture until the sixth to twelfth day Thus it appeared that chloramphenicol interfered with the early bactericidal effects of penicillin on enterococci i e had some action antagonistic to that of penicillin This interference phenomenon was observed with all nine strains of enterococci but not always to the same degree

[In this article and the two succeeding ones there is presented a most interesting and possibly a most important problem These workers seem to demonstrate convincingly that under certain conditions one antibiotic may exert an antagonistic effect on the antibacterial action of another The problem deserves study but there is as yet no clinical evidence bearing on it. There is on the other hand good clinical evidence that certain combinations exert a synergistic effect (see this YEAR BOOK p 48—Ed.]

Joint Action of Penicillin with Chloramphenicol on Experimental Streptococcic Infection of Mice In previous studies on the effects of antibiotics on enterococci it was observed that in the presence of both penicillin and chloramphenicol the rate of bactericidal action was considerably slower than with penicillin alone In the present study E Jawetz and R S Speck[3] (Univ of California) attempted to deter

(3) P c. Soc. E p B l & M d 74 93 96 May 1950

plained by some authors by the theory that elimination of existing bacteria leaves a vacuum which is bound to be filled by others This theory certainly does not account for all cases because during penicillin treatment resistant bacteria may appear where there were no bacteria before Such an occurrence seems particularly likely in the urinary tract during excretion of penicillin given for disease elsewhere In three of the author s patients under treatment for bacterial endocarditis urinary infections due to Ps pyocyanea developed for no apparent reason other than presence of the drug in the urine

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(2) S c 111 254 256 M 10 1950

in some physical or chemical process so that the resulting complex is of lesser chemotherapeutic efficacy (2) They may compete with one another for receptors on the susceptible bacterial cells Through mass action the less effective drug may thus interfere with the more potent one (3) Possibly one drug may change developmental characteristics or properties of the infecting micro organisms so that their susceptibility to other agents is greatly diminished No definite choice can be made among these possible mechanisms

The clearcut antagonistic action between chloramphenicol and penicillin draws attention to the possibility that the action of one chemotherapeutic agent may be interfered with rather than potentiated by administering it with others It has been popular medical practice to administer several chemotherapeutic agents simultaneously in the expectation that such therapy would more rapidly and effectively terminate an infection In certain instances it has been conclusively shown that several antimicrobial drugs administered together are more effective than one alone The present study strongly suggests that the opposite may sometimes be the case If antagonistic effects between antibiotic agents play any role it may be necessary for physicians to use such drugs only in specific cases and to abandon shotgun therapy

Bacteriologic Studies of Newer Antibiotics Effect of Combined Drugs on Micro organisms Though there is a growing tendency to use combined antibiotics in infectious diseases in anticipation of more rapid elimination of the infecting organism few reports have been made and these give diverse results In recent in vitro studies with combined antibiotics both synergistic and interfering effects were observed

Studies by Sophie Spicer[4] (New York City Dept of Health) on the in vitro effect of aureomycin chloramphenicol streptomycin dihydrostreptomycin penicillin and bacitracin singly and in pairs on bacterial strains of several species indicated destructive action by each antibiotic on most organisms in a sensitive strain All antibiotics left a residuum of viable organisms differing in number and character with the antibiotic and the bacterial strain tested In any bacterial population there may be a heterogeneity of individuals just as there is in a population of other living organisms and individual

(4) J L b & Cl Med. 36 183 191 A gu t, 1950

mine whether this apparent antagonism between the two agents is limited to an in vitro phenomenon or whether it occurs in vivo Since enterococci are essentially nonpathogenic for small laboratory animals a highly fatal strain of beta hemolytic streptococci was used

Either drug alone protected all but 20 per cent of the animals whereas administration of both drugs was followed by a mortality rate of 60 per cent The table shows results when

JOINT ACTION OF PENICILLIN WITH CHLORAMPHENICOL ON STREPTOCOCCIC INFECTION*

Streptococcus $L.D_{50}$	Chloramphenicol µg	Penicillin G µg	Deaths/Total in Group	% Deaths
100	800	0	9/26	34
100	0	6	3/16	19
100	0	120	2/26	8
100	800	6	11/16	68
100	800	30	12/20	60
100	800	120	18/36	50
100	50	6	11/16	68
100	50	30	13/20	65
100	50	120	13/35	34
0	800	120	0/16	0
100	0	0	26/26	100
10	0	0	12/12	100

* M e weigh ng 20 Gm e h w e g n 100 $L.D_{50}$ of a lt e f C 203 int aperiton lly On hou l t the drug o sal ne w dm tered i t ap ri tone lly bout m ut ap rt each n a v l me of 0 ml

the chloramphenicol dose was kept constant and the penicillin dose varied Any combination of penicillin with chloramphenicol was followed by a much larger number of deaths than the same dose of either drug alone particularly penicillin alone However with any chloramphenicol dose the more penicillin was administered the lower was the death rate

Chloramphenicol and penicillin administered to uninfected mice either alone or together gave no evidence of toxicity Consequently the higher death rate with joint use of both drugs in infected animals cannot be attributed to toxic depression of the host s defense mechanism nor to direct toxic action of a drug The only possible conclusion is that penicillin and chloramphenicol interfere with each other in some manner

This interference or antagonism may take place in one of three ways (1) The two drugs may interact with one another

or utilization of members of the B complex. Henry M. Gewin and George J. Friou[5] (Yale Univ.) report the following case because it not only illustrates many of the side effects previously described but also demonstrates the occurrence of peripheral neuritis, optic neuritis and severe gastrointestinal bleeding associated with prothrombin deficiency and x-ray changes in the intestinal mucosa.

Man, 22, complained of headache, chills and fever. He had a history of acute rheumatic fever at age 7 and four recurrences. Acute bacterial endocarditis with multiple emboli and rheumatic heart disease with cardiac enlargement, mitral stenosis and insufficiency were diagnosed. Blood cultures showed 800 colonies of Staphylococcus aureus/cc. Because of lack of improvement after 24 hours of penicillin therapy and because the infecting organism was found to grow in 1,000 units of penicillin/cc., aureomycin was started in an initial dose of 3 Gm. followed by 0.25 Gm. every two hours. Sensitivity reports indicated that the organism was inhibited by 25 μg./cc. chloramphenicol or 32 μg./cc. aureomycin. Low grade staphylococcemia persisted despite disappearance of the phenomena of generalized sepsis. Therefore, two weeks after hospitalization, chloramphenicol was started with an initial dose of 3 Gm. and 0.25 Gm. every two hours thereafter. After three days of combined therapy (aureomycin and chloramphenicol) blood cultures became negative.

Eleven days after start of combined therapy, anorexia, nausea, vomiting and watery diarrhea developed and persisted despite use of dramamine® until antibiotic therapy was stopped after 33 days of aureomycin and 20 days of chloramphenicol. He remained well for four days. Chills, fever and prostration then reappeared and blood cultures were again positive. Combined therapy was reinstituted. Fever and staphylococcemia slowly subsided.

Even though there was no further evidence of infection, important symptoms occurred during the second course of therapy. Four days after combined therapy was reinstituted, erythema and excoriation of the skin over the periscrotal area were noted. Two weeks later there was distinct evidence of vitamin deficiency consisting of a red smooth tongue, diffuse pharyngeal injection and desquamating yellowish papules about the nose and ears. Within two weeks after start of a liquid vitamin preparation, all skin and mucosal lesions disappeared. However, nausea and vomiting reoccurred and the vomitus became black for the first time. Bleeding and clotting times and platelet count were normal but prothrombin time was 43 per cent of normal. X-rays revealed an atypical small bowel pattern with segmentation of barium and slight coarsening of the mucosal folds in the jejunum but no ulceration could be demonstrated. Daily intravenous therapy with vitamins K, B and C was begun along with daily intramuscular injection of liver extract.

(5) Yale J. Biol. & Med. 23:33-339, February 1951.

members may differ in ability to withstand unfavorable environments hence the finding of viable organisms after exposure to the antibiotic agent is not surprising That antibiotics operate in vivo as they do in vitro in this respect can be observed clinically No matter how spectacular the initial response relapse may follow unless the antibiotic is continued for a time The initial doses evidently destroy most of the bacteria if the strain is sensitive Subsequent doses keep the residual organisms from multiplying until the host s own defense mechanism takes over the task of clearing up the remaining infection

The effect of antibiotics used in pairs was synergistic additive interfering or indifferent depending on the particular combination of drugs for a given bacterial strain On the assumption that two antibiotics have a complementary effect on an infecting bacterial strain—in that one acts on the remaining viable organisms which the other is incapable of destroying—it seems theoretically possible to eliminate all *infecting bacteria on initial administration of such a pair of* antibiotics without having to depend on the patient s defense mechanism Such therapy would be especially valuable in patients now treated with streptomycin alone in whom resistance to the drug develops rapidly and in those requiring prolonged drug therapy However whereas one antibiotic may complement another in its action on sensitive organisms it may also impede the action of the other if not properly chosen The importance of testing the offending organism for sensitivity to the drugs before administering them simultaneously is apparent

Manifestations of Vitamin Deficiency during Aureomycin and Chloramphenicol Therapy of Endocarditis Due to Staphylococcus Aureus Many side effects noted during aureomycin and chloramphenicol therapy are caused by interference with the biochemical processes involved in vitamin B metabolism In addition to the gastrointestinal symptoms of nausea and/or vomiting epigastric distress heartburn and diarrhea stools often become odorless in association with a change in the normal intestinal bacterial flora Mucous membrane manifestations closely resembling those of pronounced riboflavin deficiency are also seen These lesions have been attributed to destruction of intestinal bacteria necessary for the synthesis

confirmed by culture in most of which the disease was appar ently a direct sequel to antibiotic therapy

In 20 patients with infections of the oropharynx oral com plications followed penicillin aureomycin and chloramphenicol therapy The clinical picture was constant regardless of the method of administration Treatment of sore throat with one of the antibiotics had been followed by clearing of the infection and 24 72 hours later by a burning tongue mouth and throat The picture varied according to the stage at which the patient was observed The tongue was most frequently in



Fig —T g l n f ll w g f tb tcs (C t f Wood I W t al I A M A 14 207 211 Ja 27 1951)

volved and was thickly coated at first often with an over growth of the filiform papillae giving the appearance of a brown or black hairy tongue (Fig 2) Later the coating or hairy covering came off leaving the tongue beefy red dry and swollen with the papillae standing out in relief The tongue was tender to palpation and to contact with acid foods Sense of taste was greatly altered The buccal mucous mem brane was at first covered with circumscribed or coalesced areas of whitish exudate which could be wiped away easily In 24 72 hours this exudate came off and the buccal mucous membrane was left dry glazed and parched In the early stage the soft palate uvula aryepiglottic folds and piriform fossae were acutely reddened and edematous followed by a glazed reddened appearance with moderate edema

Antibiotic therapy was stopped after 46 days of retreatment 10 days later he had numbness and tingling of the feet slight blurring of both optic disks granular changes of the pigment layers of the retina and enlarged blind spots bilaterally Neurologic examination revealed patchy ill defined areas of diminished pain sensation along the dorsal aspect of all toes and the medial portion of the right lower leg A few days later he was discharged Visual symptoms had disappeared but numbness and tingling of the feet persisted

Five weeks after discharge he came to the emergency room because of increasingly frequent lancinating pains in the toes Neurologic examination disclosed diminished testicular pain sensation and decreased deep pain sensation of the legs Tactile sensation was diminished below the knees and absent over the toes Vibratory sensation was impaired over the legs and ankles Position sense motor functions and reflexes were normal Therapy consisting of vitamin B_{12} in doses of 30 μg twice weekly resulted in progressive improvement

The conclusion that these disturbances resulted from use of aureomycin and chloramphenicol appears warranted from the sequence of events Since both antibiotics were used neither can be held solely responsible Whether these disturbances resulted from destruction of the intestinal bacteria essential for vitamin B synthesis or utilization or whether aureomycin and chloramphenicol exert a competitive blockage of intracellular metabolism thus producing changes resembling vitamin deficiency is not known The latter possibility is in keeping with theories of the mechanism of action of the antibiotic agents in bacterial metabolism If this concept is correct parenteral administration of vitamin preparations may lessen therapeutic effectiveness of the antibiotic agents However in the present state of knowledge the withholding of vitamins appears unwise

[This seems rather convincing that prolonged therapy with the two antibiotics caused the deficiency manifestations described We should be alert for such side effects especially in patients undergoing prolonged treatment—Ed]

Monilial Infections Complicating Therapeutic Use of Antibiotics It has been frequently observed that when mixtures of bacteria are exposed to various antibiotics susceptible organisms are suppressed or removed whereas nonsusceptible organisms may grow abundantly even in the presence of high concentrations of the antibiotic agent Recently James W Woods Isaac H Manning Jr and Carl N Patterson[6] (Durham N C) observed a number of cases of clinical moniliasis

(6) J A M A 145 207 211 Ja 27 1951

including (1) direct stimulation of growth of candida by the antibiotic (2) suppression of growth of bacteria and other organisms competing with candida for nutritive substances in the environmental substrate (3) change in the pH of the environment through alteration in bacterial flora and (4) change in host tissue resistance as the result of vitamin deficiency or some other physiopathologic change In vitro studies of four strains of candida showed that these antibiotics had no stimulating or suppressing effect on rate of growth Suppression of bacterial flora coexisting with candida and competing for nutrition in the same substrate was thought to be the most probable cause for monilial overgrowth and host infection Clinical observations do not permit conclusions regarding the importance of changes in vitamin biosynthesis or other physiopathologic reactions lowering host resistance to monilial invasion Nevertheless treatment with vitamin B complex seems to have some therapeutic value

[It is difficult to prove that the manifestations described were due to monilial infection the mere presence of monilia does not establish it as the cause of the trouble Nevertheless the possibility is reasonable —Ed.]

Failure of Absorption of Aureomycin and Terramycin Administered as Retention Enema Murray S Hoffman William E Wellman and Wallace E Herrell[7] administered aureomycin and terramycin rectally to 11 patients with normal hepatic and renal function and normal lower intestinal tract Each dose of 1 or 2 Gm was suspended in 30 cc water and given in the form of a retention enema All patients were observed carefully to make certain that the enemas were retained for at least four hours Neither aureomycin or terramycin was absorbed into the blood in detectable quantities

[This is useful information One would like to see similar studies done on infants since rectal administration is likely to be desirable in *young* patients It seems established that infants can absorb chloramphenicol from the rectum —Ed]

ACTH AND CORTISONE IN INFECTION

Effects of Adrenocorticotrophic Hormone in Pneumonia Clinical Bacteriologic and Serologic Studies of three patients with pneumococcic (types VIII II and I) and two with pri

(7) Proc Staff Meet Mayo Clin 25 463 464 Aug 2 1950

Three patients with diarrhea and an unusually heavy growth of Candida albicans in the stools were studied The presenting complaint was persistent diarrhea which developed after treatment with antibiotics of some infection not related to the gastrointestinal tract The diarrhea was mild with passage of three to six loose watery or mushy stools daily occasionally containing mucus and rarely blood This symptom complex was noted in one patient after prolonged penicillin therapy in one after aureomycin therapy and in one after both aureomycin and penicillin therapy In addition three patients treated with aureomycin or chloramphenicol did not *have diarrhea but stool culture revealed* an abundant *growth* of C albicans Presence of these organisms in such heavy concentration was considered significant

In two patients given antibiotic therapy for acute and chronic pulmonary infections bronchopulmonary moniliasis developed This form of monilial infection presents a problem in choice of therapy for patients with respiratory tract infections in which C albicans coexists with some acute or chronic bacterial infection

Woman 61 was hospitalized with a history of bilateral lower lobe pneumonia six weeks previously treated with massive doses of *penicillin and aureomycin Improvement had been gradual but during therapy* severe acute arthritis developed Examination revealed signs of consolidation at the bases of both lungs and acute redness and swelling of multiple joints of the extremities with limitation of motion A chest x ray revealed rather extensive *mottling* extending from the lower portion of both hili into the lung bases The pneumonitis failed to improve and sputum cultures were positive for C albicans

A rabbit inoculated with the organism died of extensive miliary involvement of the kidneys within three days The patient was given a skin test with monilial vaccine and a strongly positive reaction was *obtained with 1 100 dilution Agglutinations for C albicans* with the patient s serum were positive in a dilution of 1 160 Bilateral pleural effusion developed with fever and increased malaise Several thoracenteses were performed with removal of sterile straw colored fluid Treatment was begun with monilial vaccine in a dilution of 1 10 000 and was carried through dilutions to 1 100 before institution of therapy with potassium iodide Cautious trials with chloramphenicol and dihydrostreptomycin were without clinical effect The patient was discharged after three months and continued to improve with gradual disappearance of pleural effusion

Several possible explanations for occurrence of monilial infections during *or after antibiotic therapy were considered*

Joseph E Smadel Herbert L Ley Jr and Fred H Diercks[9] thought that the toxemia of typhoid might be affected by appropriate doses of cortisone acetate Accordingly eight patients with typhoid were given cortisone and chloramphenicol Chloramphenicol was given orally to adults in an initial dose of 3 0 Gm followed by 1 5 Gm at 12 hour intervals nine times after which 1 5 Gm was administered once daily for 10 or 11 days Cortisone was administered according to one of two schedules Four patients received 200 mg during the first 24 hours followed by 100 mg daily for three days Four were given 300 mg the first day 200 mg the second and 100 mg on each of the two succeeding days

Previous experience with chloramphenicol in treatment of 44 patients with typhoid had showed that an average of four days was required from the time the first dose of antibiotic was given until fever and toxemia disappeared The four patients given 300 mg cortisone and 4 5 Gm chloramphenicol during the first 24 hours were afebrile before the end of this period Three were sitting up in bed and so bright and cheerful that they seemed almost euphoric moreover they complained of hunger Response in the four patients given the smaller dose of cortisone was not so dramatic Average duration of fever in the first group was 50 2 hours in the second 15 5 hours

There appeared to be little doubt that the simultaneous administration of cortisone and chloramphenicol terminates the acute manifestations of typhoid more promptly than does chloramphenicol alone It was assumed that this is desirable Two relapses among the eight patients was a higher incidence than would ordinarily be expected in patients who had received a full two weeks course of chloramphenicol Whether this was mere coincidence or related to the supplementary use of cortisone was unknown

Treatment of Typhoid Fever Control of Clinical Manifestations with Cortisone T E Woodward H E Hall R Dias Rivera J A Hightower E Martinez and R T Parker[1] tested clinical control of typhoid in seven patients by use of cortisone alone In four adults cortisone acetate (200 300 mg for the

(9) A n I t Med 34 1 9 J 9 1951
(1) Ibid pp 10 39

mary atypical (virus) pneumonia are reported by Edward H Kass Sidney H Ingbar and Maxwell Finland[8] (Harvard Univ) Administration of ACTH to all five was followed by prompt remission of clinical symptoms associated with the acute illness but the remissions were not lasting in every case In each case hormone administration was followed in 12 24 hours by diaphoresis defervescence and striking subjective improvement *In the cases of pneumococcic pneumonia* abundant pneumococci were present in sputum after the patients were afebrile and asymptomatic and in one case bacteremia was demonstrated on two successive occasions 12 and 36 hours after the patient was clinically well Rusty sputum was raised for five days after apparent remission of the acute illness in another patient with pneumococcic pneumonia

The number of cases studied is too small for valid comparisons with data obtained in large numbers of similar cases of untreated pneumonias However it seems unlikely that the defervescence would have occurred spontaneously coincident with ACTH administration These observations suggest that ACTH may have an antipyretic action

There is no evidence that ACTH or the cortical hormones exert a direct effect on the infectious agents Antipneumococcic antibodies and cold agglutinins appeared at the anticipated time with no evidence of acceleration or delay in their production It can be concluded that the changes after administration of ACTH were due to an effect exerted on the host *and not on the etiologic agents*

[We have no good explanation for the effect of adrenal hormone on pneumococcic pneumonia *There is more to it than an antipyretic action* although that is undoubtedly one factor In view of the experimental evidence showing that ACTH and cortisone suppress the phagocytic response in acute infection one cannot even be sure this is safe practice and the authors do not recommend it We may eventually find that combined therapy ACTH or cortisone together with an effective antibacterial agent is the best therapy Such an attack is described in the next article —Ed]

Treatment of Typhoid Fever Combined Therapy with Cortisone and Chloramphenicol Although chloramphenicol has an established place in treatment of typhoid little if any clinical improvement occurs during *the first 36 hours of therapy* and patients are not afebrile until about the fourth day

(8) Ann Int Med 33 1081 1098 Nov mb 1950

therapy was followed by fall of temperature to normal levels within 100 hours after administration of the initial dose (average 36 hours) Cortisone showed no effect on the incidence of typhoid bacilli in the feces since practically all patients had positive stools during therapy Complications typical of typhoid such as perforation and hemorrhage were not seen in the six patients observed in the early stages The other patient first thought to have typhoid and treated with cortisone on the 51st day of illness had gross intestinal hemorrhage on the 60th day Figures 3 and 4 show the clinical course in two patients

The authors also treated a known typhoid carrier with cortisone Three days of therapy with a total of 500 mg cortisone did not reverse the positive bile and stool cultures for the typhoid bacillus either during or after treatment

Cortisone which seems to exert a favorable influence on the host probably achieves its effect in typhoid patients through its ability to assist the host cell since it has no demonstrable effect on Salmonella typhosa Though treatment of typhoid with cortisone alone is of theoretic interest the authors believe that chloramphenicol with its antibacterial action is still vital in typhoid management

[From the theoretical standpoint these findings are of great interest. Who would have guessed that cortisone which is without effect on the typhoid bacillus would be capable of halting so dramatically the course of typhoid fever? One might speculate that under the influence of hormone therapy the host s antibodies are better able to reach and affect the micro organisms In view of other less salutary effects of ACTH and cortisone on resistance to infectious diseases this type of work should be regarded as experimental cortisone therapy of typhoid fever is not recommended at the present time —Ed]

Effect of ACTH on Induced Fever In patients with febrile illnesses ACTH often causes prompt defervescence but fever frequently returns after ACTH or cortisone is withdrawn These hormones may heighten resistance to the toxic effects of a given illness or perhaps obscure certain disease manifestations by reducing the fever without affecting fundamental pathologic processes of the illness Edward H Kass and Maxwell Finland[2] (Boston City Hosp) studied the antipyretic effect of ACTH after artificial induction of fever in man and animals

Duration and intensity of the febrile response to injection

(2) New England J Med. 243 693 695 N 2 1950

first 24 hours in divided doses of 100 mg) was administered intramuscularly During the second 24 hours 200 mg was given and on the third day 100 mg Three children were given about half the adult dose

In six patients the mean day of illness on which treatment

Fig 3 (top) —Co t so a tat th r py n typh d p t nt w th u ev ntf l on val u e

Fig 4 (bottom) —Cort sone the py n typhoid p t nt w th r lap e followed by rap d p nse on eadm n trat n f c rt son

(Court y of Woodward T E. et al Ann. I t. M d. 34 10 19 Janu ry 1951)

was instituted was the eleventh Symptoms improved strikingly in the first 36 hours of therapy Effect on the febrile course gave further evidence that cortisone influences the course of typhoid In six of the seven patients irrespective of age height of the preceding fever or day of disease cortisone

Changing Nature of Pneumonia is discussed by Hobart A Reimann[4] (Jefferson Med College) Cure of many bacterial pneumonias with sulfonamide compounds and antibiotics has led to an impression that the nature of pneumonia in general has changed greatly in the past decade Although the mortality rate has been reduced it is not certain that the incidence and nature of untreated acute pulmonary infections have changed in proportion

Lobar pneumonia was never common At a large city hospital in Philadelphia in 1936-37 261 lobar pneumonia patients were admitted as compared with 312 in 1945-46 On Reimann's hospital service 75 patients were admitted in 1937-40 and 91 in 1946-49 Modern therapy has not materially changed the incidence of pneumococcic pneumonia nor does the distribution of types of pneumococci appear much different now than in previous years Since the relative incidence and predominance of types varied from year to year even before 1939 recent studies showing decrease in number of type 1 cases and increase in those of higher numbered types do not indicate great change Lobar pneumonia now appears to affect older age groups but this may be due to successful prevention or therapy in younger adults and unchanged or increasing incidence in older persons due to complicating degenerative or other diseases Surprisingly modern therapy has not reduced the number of complications to the degree expected However all observers agree about the decline in mortality rate of lobar pneumonia It was 20-40 per cent in the preantiserum and presulfonamide days and now as a result of therapy with penicillin is 5 7 9 3 per cent

Whereas pneumococcic lobar pneumonia is usually a sporadic endemic disease with a remarkably uniform incidence from year to year pneumonias caused by secondary bacterial infection during epidemics of influenza and pneumonias caused by presumed viruses come and go in epidemic waves at unpredictable intervals When the viruses are temporarily prevalent the usual pattern of pneumonia changes This

(4) Ann Int Med 33 1246 1253 Nov 1950

of typhoid bacilli in man were reduced by previous administration of ACTH Febrile response of rabbits to injections of typhoid bacilli or influenza virus was similarly reduced This antipyretic action of ACTH may enable some patients to respond *with reduction in fever but no alteration of the fundamental* pathologic processes of the basic illness How ACTH exerts its antipyretic effects is not clear The relation between the hypothalamus and the hypophyseal production of ACTH suggests that the steroid hormones may alter the activity of the hypothalamic heat regulating centers Good clinical responses to ACTH or cortisone require close scrutiny to determine which represent alterations in the fundamental processes of the disease after administration of the hormones and which reflect the antipyretic and possible analgesic action of these potent agents

[Not only fever but other cardinal signs of inflammation such as pain erythema, tenderness and swelling are suppressed by ACTH and cortisone Consequently we must be especially vigilant for signs of infection in persons receiving these hormones Already there are a number of reports of such serious entities as peritonitis pneumonia and pericarditis escaping detection because of the absence of pain fever etc under the influence of ACTH or cortisone.—Ed]

Effect of Cortisone in Sarcoidosis Because it tends to involve many organs sarcoidosis resembles clinically certain of the disseminated collagen diseases that have responded to the glucocorticoids Hence Maurice Sones Harold L Israel Mary B Dratman and Jesse H Frank[3] (Woman s Med College of Pennsylvania) studied two patients with severe and widespread sarcoidosis to detect possible subclinical endocrine impairment and to determine the effect of cortisone therapy

Endocrinologic study gave some evidence of impaired adrenal function Both patients had diminished 17 ketosteroid excretion one had abnormal eosinophil response to epinephrine and one low water excretion index Prompt and striking improvement in pulmonary cutaneous lacrimal parotid and lymph node lesions in both patients after cortisone therapy was probably not coincidental Biopsy revealed striking tissue changes after treatment

[We too have observed *amelioration of the manifestations of sarcoidosis* following cortisone therapy It is disappointing however to find that the signs usually return shortly after discontinuing the treatment —Ed]

(3) New Eng J Med 244 09 13 Feb 8 1951

fectual in acute primary klebsiella pneumonia Although the effectiveness of streptomycin against these infections has been reported only 10 cases were found in the literature on use of streptomycin in acute primary klebsiella pneumonia in adults These showed a definite improvement over previously reported survival rates Heretofore it was estimated that approximately one sixth of patients with klebsiella pneumonia recovered about a third progressed to the chronic phase (fibrosis bronchiectasis and/or cavitation) and about a half died

Maurice Nataro David Shapiro and Armond T Gordon[6] (Univ of Louisville) treated four patients with acute primary lobar pneumonia due to K pneumoniae with streptomycin These 4 and the 10 cases from the literature show a decrease in number of patients whose disease progresses into the chronic phase only 2 of the 14 patients having x ray evidence of cavitation or severe fibrosis at time of discharge or on follow up One of the authors four patients died However death occurred less than 24 hours after start of streptomycin therapy and the patient cannot be considered to have had an adequate trial of the drug Recommended streptomycin dosage schedule is 0 4 Gm every 4 hours for 7-10 days

Because of the toxic effects of streptomycin and because aureomycin has shown promise in experimental Friedlander infections the authors tried it on a fifth patient with K pneumoniae infection

Man 28 was becoming clinically worse and x rays revealed massive spread of pneumonic process despite penicillin therapy Thirteen days after onset aureomycin therapy was started Results were dramatic Within 24 hours there was decided clinical improvement and after the second 24 hours temperature was normal X rays a week later showed more rapid improvement than was usual after treatment with streptomycin for the same time interval

Although x ray evidence is not diagnostic it may be highly suggestive and lead to early discovery of K pneumoniae in sputum or blood permitting prompt therapy with streptomycin or aureomycin which appear to be most effective agents in this disease

[Although no one clinic ever seems to have enough cases of Friedlander pneumonia to carry out a good evaluation of therapeutic agents there s reason to believe that streptomyc n aureomycin terramycin and

(6) J A M A 144 1216 S pt 2 1950

atypical pneumonia is illustrated by the pandemic of viral pneumonia in 1941-43 Viral pneumonias at that time represented the severest forms of a mild infection of the respiratory tract and appeared in the proportion of 1 pneumonia to 10 non pneumonic mild cases The pneumonias themselves appeared three to four times as often as lobar pneumonia but the mortality rate was less than 1 per cent No large outbreaks of viral pneumonia have been recorded since then but in keeping with other epidemic diseases recurrence may be anticipated

Etiologic diagnoses should be made in all cases of pneumonia since different entities need different antibiotic therapy Several key diagnostic centers strategically placed as observation posts throughout the country should continue to determine the causes of all forms of pneumonia as they appear and the type of pneumococcus prevalent

[It is natural to gain the impression that pneumococcic pneumonia is changing since most cases are now aborted by therapy before the classical picture of the disease can develop Furthermore fewer cases are seen in hospitals because patients can usually be cared for satisfactorily at home —Ed]

Observations on Staphylococcic Pneumonia during Influenza Epidemic of January February 1949 are reported by W J Bruins Slot[5] (Zuider Hosp Rotterdam) Of 37 patients hospitalized for pneumonia during the influenza epidemic Staphylococcus aureus was the causative organism in 17 These 17 patients received high doses of penicillin intramuscularly as well as by spray dosage varying from 1 000 000 to 8 000 000 units daily One patient died in diabetic coma 16 recovered Large abscesses did not develop

In 14 patients with staphylococcic pneumonia blood serum was examined for influenza A and B by the complement fixation test in 8 the hemagglutination inhibition test was also carried out Results of serologic examination were positive for influenza A in 11 patients and for influenza B in 1

[Staphylococcic pneumonia in adults is rarely observed except in the wake of an influenza epidemic —Ed]

Acute Primary Klebsiella Pneumonia Management of lobar pneumonia due to Klebsiella pneumoniae (Friedländer s bacillus) continues to offer a real challenge In 1945 reports indicated a mortality of 51 97 per cent in contrast with the dramatic response of other bacterial pneumonias to the antibiotics The sulfonamides and penicillin are relatively inef

(5) Nederl t jdschr g nee k. 94 3438 3451 D c 2 1950

level in the cerebrospinal fluid of patients with bacterial meningitis is often of diagnostic value in differentiation of bacterial from aseptic meningitis Reasons for the reduced glucose concentration are unknown although it has been stated that the main factor is utilization of glucose by bacteria growing in the fluid On the other hand the glucose concentration in aseptic meningitis is said to be normal because the *leukocytes do not metabolize it The object of the investigation* reported by Sidney Goldring and Carl G Harford[8] (Washington Univ) was to assess the importance of bacterial growth and leukocytic metabolism as factors tending to lower the glucose level

Glucose levels in the cerebrospinal fluid of dogs with aseptic meningitis were normal whereas incubation in vitro of such fluids resulted in consumption of glucose Large numbers of pneumococci growing rapidly in normal cerebrospinal fluid were needed to consume glucose at rates approximating those at which glucose was utilized in vitro by fluids of dogs with aseptic meningitis

An adequate explanation of the discrepancy between in vitro and in vivo glucose levels appears to be that the glucose is replenished by the body more rapidly than it is utilized by the leukocytes Since normal replenishment mechanisms appear to suffice to maintain the glucose level when leukocytes are present without bacteria and the number of bacteria in the cerebrospinal fluid in meningitis is usually much smaller than that used in the in vitro tests additional factors apparently cause the lowered glucose level Other possible mechanisms are change in permeability of the blood cerebrospinal fluid barrier or damage to meninges and choroid plexus may increase *their glycolytic rate There is no direct experimental* evidence to support these theories

[Of special interest is the low sugar level of the cerebrospinal fluid in tuberculous meningitis The slow growing tubercle bacilli would not be expected to utilize sugar rapidly and the cellular content of the fluid is *not different from that found in viral meningitides* where the glucose content is normal Possibly one of the last possibilities suggested by the authors is responsible —Ed]

(8) Proc Soc Exper Biol & Med 75 669 672 December 1950

chloramphenicol are all effective in therapy Which drug or drugs is the treatment of choice cannot be stated at this time Statistics based on 10 scattered case reports are not reliable because people tend to report successes not failures The important clinical point is to recognize Friedlander pneumonia early to avoid loss of precious time by treating with penicillin For this reason the sputum should always be examined by Gram stain and by culture Most cases of Friedlander pneumonia occur in males over age 50 —Ed]

MENINGITIS

Meningitis Due to Simultaneous Double Infections in Children Edwin B Vaden E Clarence Rice and Vera Stadnichenko[7] (Children s Hosp Washington D C) observed 10 patients with simultaneous double infection of the meninges among 124 patients treated for purulent meningitis in 30 months All patients were 5 years or under five being less than 1 year old In 9 of the 10 patients Hemophilus influenzae (type B in 8 type A in 1) was one of the offending organisms One patient had meningitis due to Diplococcus pneumoniae and Escherichia coli The influenza bacillus was associated with Neisseria intracellularis in four cases streptococcus in three and D pneumoniae in two Blood cultures were taken on hospitalization of all patients Three patients had mixed bacteremia the organisms being identical to those recovered from cerebrospinal fluid Three others had positive blood cultures with only one of the offending organisms being isolated

All patients received fluids parenterally whole blood sulfadiazine and penicillin Streptomycin was given most patients with H influenzae infection There were no deaths Seven were discharged with no apparent damage to the central nervous system

Because of the high incidence of double infection it is suggested that every child with purulent meningitis be treated for a mixed infection until bacteriologic studies are completed

[This situation is not commonly recognized possibly because of the tendency to suspect mixed cultures as representing contaminations Proof of double infection in these cases would have been strengthened by demonstrating development of antibodies to both organisms during convalescence.—Ed]

Effect of Leukocytes and Bacteria on Glucose Content of Cerebrospinal Fluid in Meningitis The subnormal glucose

(7) J A M A 143 140 1404 Aug 19 1950

level in the cerebrospinal fluid of patients with bacterial meningitis is often of diagnostic value in differentiation of bacterial from aseptic meningitis. Reasons for the reduced glucose concentration are unknown, although it has been stated that the main factor is utilization of glucose by bacteria growing in the fluid. On the other hand the glucose concentration in aseptic meningitis is said to be normal because the leukocytes do not metabolize it. The object of the investigation reported by Sidney Goldring and Carl G. Harford[8] (Washington Univ.) was to assess the importance of bacterial growth and leukocytic metabolism as factors tending to lower the glucose level.

Glucose levels in the cerebrospinal fluid of dogs with aseptic meningitis were normal, whereas incubation in vitro of such fluids resulted in consumption of glucose. Large numbers of pneumococci growing rapidly in normal cerebrospinal fluid were needed to consume glucose at rates approximating those at which glucose was utilized in vitro by fluids of dogs with aseptic meningitis.

An adequate explanation of the discrepancy between in vitro and in vivo glucose levels appears to be that the glucose is replenished by the body more rapidly than it is utilized by the leukocytes. Since normal replenishment mechanisms appear to suffice to maintain the glucose level when leukocytes are present without bacteria and the number of bacteria in the cerebrospinal fluid in meningitis is usually much smaller than that used in the in vitro tests, additional factors apparently cause the lowered glucose level. Other possible mechanisms are: change in permeability of the blood-cerebrospinal fluid barrier, or damage to meninges and choroid plexus may increase their glycolytic rate. There is no direct experimental evidence to support these theories.

[Of special interest is the low sugar level of the cerebrospinal fluid in tuberculous meningitis. The slow growing tubercle bacilli would not be expected to utilize sugar rapidly and the cellular content of the fluid is not different from that found in viral meningitides, where the glucose content is normal. Possibly one of the last possibilities suggested by the authors is responsible.—Ed.]

(8) Proc. Soc. Exper. Biol. & Med. 75: 669-672, December, 1950.

BACTERIAL ENDOCARDITIS

New Method for Production of Experimental Bacterial Endocarditis It has been shown that discontinuous exposure of rats to simulated high altitudes of 25 000 ft may produce fibrinous vegetations and thickening of the heart valves The vegetations except for absence of infection are essentially similar to those found in human bacterial endocarditis Because of this similarity and because bacterial endocarditis in man is confined chiefly to previously damaged valves Benjamin Highman and Paul D Altland[9] (Nat l Inst of Health Bethesda Md) considered it possible that rats with heart valves damaged by exposure to altitude would be particularly suitable for study of experimental bacterial endocarditis Several groups of rats were exposed four hours daily to a simulated altitude of 25 000 ft After three to six months they received following their daily exposure to altitude an intravenous injection of streptococci four times weekly for three weeks In each experiment a group of 10 altitude rats and 10 nonaltitude rats (controls) were given in random order 0 5 ml broth from the same culture tube at each injection Tail blood cultures were generally made 24 hours after the 2d 6th and 12th injections

Sixty two per cent of the altitude rats died before completion of 12 injections of streptococci and in 66 per cent endocarditis developed in contrast only 9 per cent of control rats died and only 15 per cent had endocarditis Endocarditis could be predicted before death in nearly all altitude rats by development of a positive blood culture associated with progressive weight loss Bacterial vegetations were found on about 54 per cent of the mitral valves observed and on 31 per cent of the aortic valves in some instances they were present on both valves or on the mural endocardium of the left atrium The authors suggest that altitude rats may be used to study the reaction and to test the effectiveness in vivo of various therapeutic measures against specific strains of organisms causing bacterial endocarditis

[This might be a useful tool for experimental work on chemotherapy and pathogenesis of bacterial endocarditis —Ed]

(9) Proc. Soc. Exper B l. & Med 75 573 577 November 1950

Treatment of Subacute Bacterial Endocarditis with Penicillin. Between August 1946 and August 1949 E. F. Hueb and H. Saexinger[1] (Univ. of Vienna) treated 100 patient Bacteriologic studies showed 64 cases due to *Streptococcus viridans*, 2 to enterococcus and 1 to nonhemolytic streptococcus. In 15 of 18 patients in whom susceptibility to penicillin was tested, the organisms were sensitive to concentration of 0.01-1.25 units/cc. Two patients with resistant organism responded to streptomycin; one patient died a few days afte the start of treatment.

Of 10 patients given 170,000-300,000 units day, 2 were cured; 5 of 15 patients receiving 400,000-600,000 units/day were cured; and 48 of 75 patients given 800,000-5,000,000 units daily recovered. In general, results improved greatly when at least 1,000,000 units, and often two or three times this amount, were given daily as indicated. Usually penicillin G was administered intramuscularly every three hours (occasionally in the "depot" form) after the fourth day of hospitalization following repeated blood cultures. In two thirds of the patients rheumatic endocarditis had preceded the subacute bacterial endocarditis and 2 patients had congenital heart disease; no pre-existing heart disease was discovered in 30 patients. Occasionally medical treatment was not sought for several months after onset. When onset was fulminating, 5,000,000 units and more were given daily from the first day on. In 17 cases an upper respiratory infection, influenza, osteomyelitis, tonsillectomy or tooth extraction preceded onset, and 2 patients had been pregnant just before onset.

Treatment was continued for at least two weeks after disappearance of all clinical and bacteriologic evidence of infection. Despite vigorous treatment with appropriate drugs, 18 of 26 patients with cardiac decompensation on hospitalization died. Even when the infection is controlled, severe decompensation usually leads to death. Of the entire group, 34 died of myocardial insufficiency.

Of 15 patients with recurrences, 9 died. All were observed from a few days to several weeks after discontinuance of penicillin. Three patients had reinfection (with a different organism) in 7, 12 and 14 months; only one was cured.

[The authors' finding that doses of penicillin in excess of 1,000,000

(1) W[illegible] kl. W[illegible] 62:738-740, Sept. 29, 1950.

units/day are desirable is in line with general experience in this country The presence of congestive failure at the beginning of treatment is a bad prognostic sign whatever the infecting organism or the scheme of treatment used —Ed]

Speculations on Mechanism of Cure of Bacterial Endocarditis Although subacute bacterial endocarditis can usually be cured by prolonged and intensive penicillin therapy Thomas H Hunter[2] (Washington Univ) states that a significant number of patients especially those with enterococci in the vegetations proves refractory to the usual course of therapy In addition it is both costly and inconvenient

The central problem of chemotherapy in bacterial endocarditis seems to be the killing of virtually all bacteria in the vegetation It is poorly vascularized and composed of fibrin and necrotic valve substance in which masses of bacteria are growing some well in the depths where metabolic exchange with the blood stream must be slow and only a few leukocytes are present Host factors alone practically never eradicate this infection Sulfonamide penicillin aureomycin or terramycin therapy may result in cure but there are reports of a high incidence of failure even though the infecting organism is highly sensitive to these antibiotics in vitro The clinical course is often prolonged with persistence of positive blood cultures temporary remission of symptoms and a high incidence of relapse If direct killing of organisms by antibiotics is important in cure of bacterial endocarditis sensitivity tests which measure only growth inhibition may be exceedingly misleading in that certain antibiotics may inhibit but not kill whereas others may appear of little value on the basis of inhibition test results yet prove to be potent accelerators of the bacterial effects of another agent

There is clinical evidence that penicillin and streptomycin together may be more effective than either drug alone in resistant cases of nonhemolytic streptococcic endocarditis In 1946 Hunter reported cure of such an enterococcic infection and since then no bacteriologic failures have occurred in six similar patients treated in the same manner Other investigators have reported identical experience If the analysis of the mechanisms involved in cure is correct and if penicillin and streptomycin are bactericidal in vivo it may prove possible to cure this infection more regularly and in a shorter

(2) J A M A 144 457 Oct 14 1950

time by combined use of the drugs A clinical experiment was initiated in which patients were being treated for 10 days with penicillin and streptomycin the first three were doing well more than 1 month after cessation of therapy

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COLON BACILLUS INFECTION

Neonatal Diarrhea and Vomiting Outbreaks in Same Maternity Unit *In 1945 association of a particular serologic type of Bacterium coli with infantile gastroenteritis was noted* Alan C Kirby Edward G Hall and William Coackley[3] (Liverpool) report an outbreak of neonatal diarrhea and vomiting associated with a strain of Bact coli serologically identical with that noted in 1945 (Bact coli D 433)

There were 144 infants at risk in the maternity unit involved Of the 12 infants in the premature unit 10 became ill since all had spent 12 24 hours in the main nursery before being transferred to the premature unit the infection may have been contracted there although it is equally likely that one or more of the infants with the first cases were infected in the main nursery and carried the infection into the premature unit A profuse growth of Bact coli D 433 was obtained from rectal swabs of all 10 infants who had diarrhea and vomiting Those of the two who remained well were negative Of the 132 infants in the main nursery 7 became ill and rectal swabs from all 7 showed Bact coli D 433 Of 12 healthy babies with positive rectal swabs on discharge from the hospital 7 became ill at home within nine days the other 5 remained well during follow up Six other infants became ill after discharge and on rehospitalization rectal swabs were positive for Bact coli D 433

Clinical illness of the 30 infants varied from mild with little constitutional disturbance to great severity Characteristic first symptom was unexplained failure to gain weight Diarrhea and vomiting started simultaneously in 11 infants Stools generally watery varied in color from bright yellow to green presence of mucus was fairly constant In severe cases dehydration developed rapidly and the infants became

(3) Lancet 2 201 207 Aug 5 1950

listless and apathetic Pyrexia was inconstant Thirteen infants are known to have died there was little difference in death rates of mature and premature infants There was no significant illness in the mothers of these babies or in the hospital staff at the time of the outbreak

To determine pathogenicity of Bact coli D 433 in adults three volunteers were given a dose of strain A (taken from subcultures kept for long intervals on agar plates at room temperature) and three were given a dose of strain B (a fairly recent subculture of the refrigerated agar slope stock culture) In each instance the dose was given in milk one to two hours after lunch Of those given strain A all three had diarrhea and abdominal discomfort the following morning with mild anorexia but no vomiting Symptoms abated during the afternoon and the volunteers were well the next day The feces of all three showed profuse growths of Bact coli D 433 after 24 hours None of those given strain B had symptoms

All 30 cases were associated with Bact coli D 433 and none of the 109 infants whose swabs remained negative had diarrhea or vomiting Seven infants infected with the strain never became ill but even if it is assumed that the total number of symptomless positives was twice as large the ratio of *sick to well (though positive for Bact coli D 433) would be* 2 1 which is not unusual in salmonella outbreaks From available evidence it appears unlikely that Bact coli D 433 is a normal commensal in the neonatal or infant population as a whole Therefore it is concluded that Bact coli D 433 was closely associated with diarrhea and vomiting in this epidemic and was probably responsible for it either alone or in close symbiosis with some other agent

[This serologic strain of colon bacillus has also been found in association with neonatal diarrhea in Buffalo by E Neter and C N Shumway (Proc Soc Exper Biol & Med 75 504 507 November 1950) Its discovery seems to be an important contribution to the knotty problem of infantile diarrhea —Ed]

Bacillus Coli Septicemia in Laennec s Cirrhosis of Liver Robert L Whipple Jr and J Frank Harris[4] (Emory Univ) report two cases Although the foreign literature contains references to this condition no cases are reported in the American literature of the past 20 years

CASE 1 —Man 47 with a history of excessive alcohol consumption and neglect of proper food intake of many years duration was

(4) Ann I t Med 33 46 466 A g t 1950

hospitalized for obvious ascites and edema of the legs There were slight icterus numerous typical spider angiomas demonstrable fluid wave and shifting dulness in the abdomen and a liver edge palpable 3-4 cm below the costal margin Laboratory data were consistent with a diagnosis of cirrhosis The usual dietary treatment was instituted After the second paracentesis was done on the 17th hospital day he became thirsty restless and had a hard shaking chill with temperature rise to 104 F Pure cultures of gram negative rod later identified as B coli grew in blood samples

CASE 2—Man 49 chronic alcoholic had noted progressive swelling of the lower part of the legs occasional attacks of right upper quadrant pain jaundice nausea and vomiting for a year The morning of hospitalization he vomited five times and the vomitus contained streaks of bright red blood During the previous eight hours he had had frequent hard shaking chills and felt feverish Examination revealed temperature of 102 F moderate icterus numerous spider angiomas typical liver palms moderate distention of and a fluid wave in the abdomen Icterus index was 55 units cephalin flocculation 4 + Blood culture was positive for B coli Despite transfusions and streptomycin therapy he died a month later Autopsy revealed typical Laennec s cirrhosis

It is believed that at times the portal circulation contains organisms which enter from the intestinal wall Furthermore the role of the liver as a bacterial filter has been demonstrated and it has been concluded that the reticuloendothelium of the liver acts as the filter In cirrhosis the portal circulation can in effect be replaced and the arterial collaterals carry blood previously drained by the portal system The assumption seems justified that the reticuloendothelial system of a cirrhotic liver is either decreased in amount or ineffective because of the circulatory changes A deficiency of effective reticuloendothelium or the circulatory changes may account for the occurrence of B coli septicemia in this disease

After this paper was submitted for publication the authors observed two additional cases of B coli septicemia in Laennec s cirrhosis of the liver

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SALMONELLA INFECTION

Fatalities in Salmonella Infections are evaluated by Ivan Saphra (Beth Israel Hosp New York City) Almost 5 000 salmonella cultures identified in the New York Salmonella

(5) Am J M S 2 0 7477 July 1950

Center in 1939-49 were reviewed After those of typhoid pa tients military personnel and persons without an adequate diagnosis were excluded there remained 3 279 salmonella infections with 174 fatalities Tables 1 and 2 show the types of salmonella involved

Age distribution in the fatal cases was significant Thirty four infants under age 1 died principally of meningitis and

TABLE 1 —SALMONELLA CULTURES ISOLATED FROM FATAL CASES*

Type	Fatal (total)	Type	Fatal (total)
S typhimurium	63 (1 155)	S litchfield	2 (11)
S choleraesuis	40 (188)	S poona	2 (12)
S oranienburg	15 (274)	S wichita	2 (4)
S newport	14 (340)	S thomp on	1 (24)
S enteritidis	5 (70)	S daytona	1 (1)
S bareilly	4 (65)	S muenchen	1 (22)
S montevideo	3 (198)	S bovis morbificans	1 (14)
S panama	3 (113)	S eastbourne	1 (5)
S anatis	3 (121)	S javiana	1 (1)
S paratyphi B	2 (143)	S newington	1 (46)
S derby	2 (99)	S havana	1 (2)
S paratyphi C	2 (5)	S worthington	1 (2)
S manhattan	2 (30)	S arizona†	1 (1)
		Total	174

Th figures n p enth d cat the total n mbe f lt es of the same type f wh ch d q ate d gn s wa g

†S lmo lla on has been el m ated f m th K ffm n Wh t S l m e ted n th a gro p of the pa lon bac ll

TABLE 2 —CULTURES ISOLATED FROM FATAL CASES IN RELATION TO TOTAL NUMBER

TYPE	N OF C URE	F T C	%
S typhimurium	1 155	63	5 2
S choleraesuis	188	40	21 3
S oranienburg	274	15	5 5
S newport	340	14	4 1
Other types (22)	1 322	42	3 2
Total	3 279	174	5 3

severe diarrhea only 10 aged 1 10 and 42 aged 10 50 Beyond age 50 mortality rose sharply with 70 deaths Computed on all cultures for the respective age groups mortality was 15 per cent for the group over 50 5 8 per cent for the infant group and about 2 per cent for the group aged 1 50

The most frequently recorded clinical diagnoses in fatal cases were acute gastroenteritis with fever vomiting and diarrhea involvement of lungs and pleura meningitis septi cemia *without further* qualification typhoidal syndromes not caused by Salmonella typhosa bacterial endocarditis

to eliminate serum reactions which are apt to be most severe in extremely sick patients

[These results are amazingly good and certainly call for further trials of chloramphenicol in H influenzae meningitis Streptomycin aureomycin and terramycin are also effective It looks as if serum therapy will go out of style —Ed]

Acute Obstructive Laryngotracheitis and Laryngotracheobronchitis Report of Outbreak is made by John O Forfar Kenneth R Keay and James Thomson[7] In Dundee a city of 182 000 inhabitants 13 cases of acute obstructive laryngotracheitis and 9 of acute obstructive laryngotracheobronchitis occurred in August to November 1949 Nine were severe seven moderate and six mild Age incidence was from 4 months to 9 years

In all patients respiratory distress was of sudden onset and in none had it been present over 24 hours before hospitalization One child was brought in because the mother thought something had stuck in his throat In some respiratory distress began without previous symptoms In others coryza cough or slight hoarseness had been present for a few days A few older children complained of sore throat and headache Onset of respiratory distress was generally associated with a croupy cough

On hospitalization the two outstanding features were respiratory distress and prostration The children were struggling for breath stridor inspiratory and expiratory was severe and in many there were the restlessness constant changing of position and anxious facies associated with anoxia Sleeplessness was pronounced Suprasternal recession and indrawing of the intercostal spaces and epigastrium were usually present Obvious cyanosis was not a feature but there was an ashen pallor which was not improved by tracheotomy in severe cases Temperature and respiration were 98 4 104 6 F and 28 66/minute respectively Tachycardia was invariably present Inspection of the throat revealed either no abnormality or moderate injection A considerable amount of mucopus was occasionally present When laryngoscopy was performed it revealed inflammation and edema of the larynx with or without mucopurulent exudate No membrane was seen Examination of the chest was often difficult because of restlessness and stridor In some cases it revealed normal

(7) Lan t 1 181 185 Ja 27 1951

breath sounds in others diminished air entry broncho vesicular or bronchial breath sounds rhonchi or moist rales The percussion note was usually resonant X rays showed normal lung fields bronchitic change or occasionally terminal bronchopneumonia White cell count was 5 000 33 000/cu mm and unrelated to the severity or duration of the illness Swabs taken from the pharynx and later also from the site of the lesion when feasible revealed a variety of organisms none of which seemed to predominate in this outbreak

The course was short In the four patients who died total duration of illness was 10 hours to 3 days in those who re covered convalescence was established within a week Treat ment mainly consisted of humidification of the atmosphere and administration of oxygen and chemotherapeutic and anti biotic drugs with attempted instrumental relief of respiratory obstruction in three patients Tracheotomy was done in one patient 64 hours after onset of symptoms followed by intuba tion through the tracheotomy tube to suck out secretions In another it was done 14 hours after respiratory distress began In the third laryngeal intubation with attempted removal of secretions by suction was done 17 hours after he became acutely ill These three patients died

Macroscopically at autopsy inflammation and edema of the larynx were the outstanding features Inflammation ex tended to various degrees downward to the trachea or bronchi and upward into the epiglottis pharynx and tonsils Histo logically there were edema hyperemia loss of epithelium and cellular infiltration These changes were maximal in the larynx but occurred also in the trachea main bronchi and epiglottis The lung showed aspiration bronchopneumonia with little interstitial inflammation When the heart was examined it showed interstitial edema without evidence of focal necrosis or cellular infiltration

The sudden onset characteristic symptoms fever and the epidemic occurrence made diagnosis easy in these cases Diphtheria obstructive laryngitis associated with the exan themas laryngitis stridulosa retropharyngeal abscess and the possibility of a foreign body in the larynx had to be consid ered The failure to respond as expected to tracheotomy was in accord with previous experience In most cases reliance was placed chiefly on supportive measures chemotherapy and anti

biotics This entailed 24-48 hours of anxious conservatism but results justified this course Some patients who recovered on conservative treatment appeared to be as severely ill as those who died and on whom instrumental relief of respiratory distress was attempted

[The etiology of this is puzzling The clinical picture described is like that of Hemophilus influenzae laryngotracheobronchitis but that organism was recovered from only one of the cases The authors seem inclined to regard the etiologic agent as a filtrable virus —Ed.]

TYPHOID FEVER

Epidemic of Typhoid Fever Luiz Montenegro[8] reports that from March to May 1950 there were probably about 100 cases of typhoid in Manaus Brazil only 59 of which were confirmed bacteriologically and reported to the health department Incidence was 1/1 000 population Bacillus typhosus was largely responsible only a few cases were caused by paratyphosus A The epidemic developed when rivers inundated lands holding human excrement An overabundance of flies was also a factor However mass vaccination of a third of the population and extermination of the flies with DDT quickly terminated the epidemic

Results with chloramphenicol were excellent in 45 of 46 confirmed cases and in 23 of 25 unconfirmed ones treatment being given at various stages of illness Average dose was 21 24 Gm Fever usually disappeared after 72 hours with remission of other symptoms Intolerance to the drug was negligible

Of the 46 patients with confirmed typhoid 4 relapsed and 1 of these with a serious renal lesion died The other three recovered after a second course of treatment Of the 25 with unconfirmed typhoid 2 relapsed but later recovered and 2 died One of the latter was severely ill for 40 days before medication was begun the other was ill 11 days before and had an intestinal perforation Had chloramphenicol been given earlier the outcome might have been different Over all death rate was 10 per cent as compared with 25 per cent in the 1949 epidemic

(8) Rev b s l m d 7 583-588 S pt mbe 1950

Aureomycin was given to 10 other patients but was discontinued because of poor results and intolerance

Synthetic and Fermentation Type Chloramphenicol (Chloromycetin*) in Typhoid Fever Prevention of Relapses by Adequate Treatment Study of 23 patients by Joseph E Smadel Charles A Bailey and Raymond Lewthwaite[9] indicates that the synthetic form of chloramphenicol is as efficacious as the natural antibiotic obtained by the fermentation process from Streptomyces venezuelae The same total amounts of either type drug are equally effective when given in divided doses at two to six hour intervals or in larger doses once or twice daily

There was a definite relation between duration of chloramphenicol treatment and occurrence of relapses Slightly more than half the patients treated for 8 days or less had a recrudescence of the disease which began about 10 days after treatment was stopped Patients treated for longer periods did not relapse The present data suggest that 14 days of treatment is sufficient to prevent relapses Despite the dramatic therapeutic effectiveness of chloramphenicol in typhoid serious complications such as intestinal hemorrhage and perforation may be expected since the stage is generally set for such developments before therapy is instituted and time is required for healing of the intestinal lesion In the present group two patients had hemorrhage sufficiently severe to produce shock Two others had intestinal perforation neither was treated surgically and chloramphenicol controlled or uppressed the usual signs of generalized peritonitis

From the present observations it appears that adequate treatment of typhoid in the adult consists of an initial oral dose of 3-4 Gm chloramphenicol followed by 1 5 Gm orally every 12 hours during the febrile period and by single daily 1 5 Gm doses for 7 days thereafter a single 1 Gm dose may be given until the fourteenth day of antibiotic therapy after which the drug may be discontinued Particular attention should be given to recognition of intestinal perforation in treated patients since the classic signs with ensuing generalized peritonitis may be partially masked by the antibacterial effect of chloramphenicol

[The recommendation of 14 days treatment ounds practical Note

(9) A I t M J 33 1 17 J ly 1950

that here and in the succeeding article intestinal perforation was handled successfully with antibiotic therapy This seems a step forward since the results of surgical drainage in this situation have always been wretched —Ed]

Typhoid Fever and Intestinal Perforation Recovery with Chloromycetin® and Dihydrostreptomycin Reid R Heffner and Arturo Brindisi[1] (New Rochelle) report a case

Man 47 was hospitalized with a generalized systemic infection of two days duration He was given 500 mg aureomycin every four hours for three doses then 250 mg every four hours On the fifth hospital day the laboratory reported isolation of Salmonella typhosus from the blood although stool culture was negative Aureomycin was discontinued and 1 Gm chloramphenicol was given every three hours for three doses then 500 mg every three hours On the ninth day after start of chloramphenicol treatment intestinal perforation developed At no time during this period did he re pond favorably to the antibiotic Daily dosage was probably insufficient but in addition his frequent refusal to take the drug and vomiting at intervals contributed to lack of favorable clinical improvement After intestinal perforation was diagnosed and 6 Gm chloramphenicol (through a Levin tube) and 1 5 Gm dihydrostreptomycin (intramuscularly) daily were begun there was decided clinical improvement within 36 hours and convalescence was uneventful The amount of chloramphenicol he actually took during the first eight days of treatment could not be determined accurately but following the intestinal perforation he received a total of 40 Gm chloramphenicol over nine days and 6 Gm dihydrostreptomycin during the first four days

Pulmonary Involvement in Typhoid and Paratyphoid Fevers Earlier medical writings display a great appreciation of the frequency with which pulmonary signs occur in enteric fevers whereas most modern textbooks merely mention that cough and bronchitis may be early symptoms and acknowledge *the possibility of later pulmonary complications* Franklin A Neva[2] (U S Naval Med Research Unit No 3 Cairo Egypt) reports observations on 49 cases of typhoid 28 of paratyphoid A 1 of paratyphoid B and 2 of paratyphoid C All patients were males aged 9 35

Pulmonary signs were noted in 64 per cent and were moderate or prominent in 42 per cent Signs most frequently found were in order of frequency rales rhonchi decreased breath sounds squeaks dulness and wheezes They tended to occur in combination These findings conform well with accepted descriptions of physical signs produced by changes in both large

(1) N w Yo k J Med 50 2966 967 D 15 1950
(2) Ann. I t. Med. 33 83 99 J ly 1950

and small pulmonary air passages They confirm the impression that whatever pulmonary signs do occur with any regularity in enteric fevers are due primarily to bronchial involvement Nine of the 80 cases were complicated by pneumonia diagnosis of which was based on clinical grounds alone in 1 case (typhoid) on autopsy observations in 3 (typhoid) and on x ray changes plus clinical data in 5 (1 of paratyphoid A 1 of paratyphoid C and 3 of typhoid)

Of 19 consecutive cases studied by serial cultures of *sputum or bronchial secretions obtained by direct aspiration* the etiologic agent was recovered in only 1 (typhoid) Pneumococci were isolated in four

The bronchial changes appear to indicate injury to the bronchial epithelium of a structural or functional nature initiated either directly or indirectly by the underlying disease Such injury could be to ciliary function or to the bronchial wall itself

Chronic Typhoid Carrier Therapy with Antagonistic Bacillus, Antibiotics and Sulfonamides Although cholecystectomy cures 70 per cent or more of biliary typhoid carriers some carriers refuse or are too ill for surgery and there are many extracholecystic carriers Therefore J A Vaichulis A Littman A C Ivy G Zubowicz and R Kaplan[3] tested various types of medical therapy at Manteno Ill State Hospital The patients had been proved carriers for an average of 5 7 years Criteria for cure consisted of eight consecutive negative stool and urine cultures made at 30 day intervals and two negative cultures of bile taken 7 days apart 30 days after the last stool examination Previous observations had indicated that frequency of spontaneous cure in the short period of therapy in this study would be so low that it would not materially affect evaluation of therapeutic results

In a study of bacterial flora in milk it was observed that contamination by certain gram positive aerobic mesophilic spore forming bacilli was accompanied by comparatively few gram negative bacteria Activity against Salmonella typhi was demonstrated on agar test plates Similar typhoid inhibiting organisms were then isolated from stools of typhoid carriers who had become cured spontaneously These organisms were tentatively identified as of the Marburg strain of Bacillus

(3) A I t M d 33 361 370 A gu t 1950

subtilis After demonstration that 100 cc doses of suspensions *of colonies of the typhoid inhibiting organisms had inhibitory* activity and could be given human subjects with no difficulty 25 patients (5 women) were given suspensions three times daily for two to four weeks and 19 were cured In two failures a second course for six weeks was successful All failures were in biliary carriers and most favorable results were obtained in patients whose infection appeared to be localized in the intestine

Synergistic therapy with massive doses of penicillin intramuscularly in combination with carinamide tresamide (a mixture of three sulfonamides) and tetraiodophenolphthalein orally was effective in 8 (19 per cent) of 42 carriers in many of whom biliary infection had been demonstrated A solution of penicillin carinamide and tresamide in 5 per cent ethyl alcohol was given intravenously in conjunction to varying extent with the aforementioned intramuscular and oral therapy for 10 days to 17 patients This had no effect in 10 patients who received less than 5 L solution Of seven who received larger amounts three were cured and three probably cured Treatment with promin® failed in six patients with aureomycin in two with chloramphenicol in two with terramycin in one and with P 38 and 510 D in four each Simultaneous administration of streptomycin orally and intramuscularly failed in three patients and was possibly successful in one.

In view of this experience and with cholecystectomy the following recommendations are made regarding management of chronic typhoid carriers based on results of cholecystography and bile cultures If calculi are seen cholecystectomy should be done If the gallbladder is visualized without stones medical therapy is likely to succeed with choice depending on results of bile cultures when bile cultures are negative bacillus therapy is indicated when positive synergistic drug therapy should be given If the gallbladder is not visualized and bile cultures are negative bacillus therapy should be tried If biliary infection is found synergistic therapy may be attempted but cholecystectomy is usually required If this fails bacillus synergistic or both may be successful

[The results obtained with the antagonistic strain of B subtilis are interesting and one would like to see it tried further by others My own experience has been that cholecystectomy is effective in more than 70 per cent of ca es —Ed]

BRUCELLOSIS

Terramycin, Chloramphenicol and Aureomycin in Acute Brucellosis Preliminary Report John H Killough Gordon B Magill and Richard C Smith[4] (Cairo Egypt) treated 39 male patients with acute brucellosis All were acutely ill and febrile had brucella agglutinations in dilutions of 1 160 or over had not received antibiotic therapy and had been ill for an average of 42 days Brucella organisms were cultured from the blood of 36 patients and from 33 Br melitensis was isolated

Terramycin was fully as effective in controlling fever as were chloramphenicol and aureomycin Terramycin treated patients became afebrile in an average of 3 4 days as compared with averages of 5 1 and 4 8 days in the chloramphenicol and aureomycin groups respectively Symptoms such as arthritis headache arthralgia and asthenia disappeared more slowly than fever in all groups Sixty nine per cent (27 patients) had at least one relapse after completion of therapy Forty six per cent (18 patients) had clinical relapse in 12 of whom it was associated with brucella bacteremia and 23 per cent (9 patients) bacterial relapse without clinical signs or symptoms Average interval from completion of therapy to onset of relapse was 16 days Of 16 patients who were re treated with larger doses of an antibiotic agent over longer periods 31 per cent relapsed again No patient had serious toxic effects Gastric disturbances often followed administration of aureomycin making terramycin or chloramphenicol more acceptable from the patient s standpoint Terramycin did not appear superior to the other compounds in prevention of relapse The frequent occurrence of bacterial relapse without signs or symptoms of illness emphasizes the value of repeated blood and urine cultures at the conclusion of therapy despite absence of clinical evidence

Chloramphenicol in Treatment of Acute Manifestations of Brucellosis Vernon Knight Francisco Ruiz Sanchez and Walsh McDermott[5] report that administration of a 6-10 day course of chloramphenicol to 13 patients with acute brucellosis

(4) J A M A 145 553 556 Feb 24 1951
(5) Am J M Sc 219 627 638 J 1950

was followed by rapid improvement which in 11 continued to complete remission Improvement in two others though definite was not as complete and the acute illness reappeared promptly when therapy was discontinued In six other patients relapse occurred one to eight weeks after cessation of therapy The two patients with incomplete remissions recovered promptly when re treated with chloramphenicol as did the one patient with a relapsing infection who received a second course of the drug

The uniformity with which acute manifestations receded after start of drug therapy was sufficiently striking to make it appear reasonable that the effects observed were attributable to the drug Thus chloramphenicol appears to exert an impressive effect on the course of acute brucellosis It is not surprising that such a short period of treatment as 6 10 days was followed by a high incidence of relapse There is ample evidence that chloramphenicol like other antimicrobic drugs seldom actually eradicates an infection Instead the drug serves to check the active progress of the infection until forces of the host can be sufficiently mobilized to exert final control If the host is unable to exert much control or if artificial suppression of the infection is relieved prematurely relapse will occur The authors advise administration of 100 mg chloramphenicol/kg daily during the acute illness followed by 25 50 mg /kg thereafter for a total arbitrarily chosen period of four to six weeks

[A treatment which fails to achieve a lasting remission in more than half of the cases is not very satisfactory Although the results would probably have been better with a longer course of therapy I suspect that much of the difficulty lies in the fact that chloramphenicol is primarily a bacteriostatic agent The problem seems to be to achieve actual eradication of the parasite —Ed]

New Method for Treatment of Brucellosis After combined use of aureomycin and dihydrostreptomycin mean colony count/whole spleen in mice infected with brucella organisms is strikingly less than that in untreated infected controls Wallace E Herrell (Mayo Clinic) and Tracy E Barber[6] (Austin Minn) report a long range carefully controlled study begun in December 1948 in which aureomycin and dihydrostreptomycin were used for culturally proved brucellosis in man Of 25 patients 21 had the bacteremic form and 4 localizing lesions with positive cultures The causative organ

(6) J A M A 144 519 524 Oct 14 1950

ism in 10 patients was Brucella abortus in 7 Br melitensis in 7 Br suis and in 1 an unidentified species of brucella The combined antibiotics were equally effective regardless of the species of brucella responsible for infection The method was used also in 10 patients with probable diagnosis of acute brucellosis even though blood cultures were not positive for brucella

Medication consisted of aureomycin hydrochloride 3 Gm/day orally in divided doses of 750 mg every six hours and dihydrostreptomycin 1 Gm intramuscularly each morning and evening In the acute bacteremic form and the acute form without positive culture this treatment was continued 12 14 days

In these 35 cases there was one symptomatic relapse but no bacteriologic relapse during follow up for 3 19 months Retreatment was not necessary in any patient This therapy is not considered specific for brucellosis but results including the absence of undesirable toxic reactions are far superior to those obtained by any previously available method

[This combination appears to be the best yet Streptomycin might be just as good as dihydrostreptomycin —Ed]

Relation of Brucellosis and Multiple Sclerosis Positive skin reactions to brucella antigen have been reported in 115 of 118 patients with multiple sclerosi studied at the Cleveland Clinic However Charles G Spicknall Leonard T Kurland B N Carle and Luther L Terry[7] obtained no positive blood culture for brucella in 112 specimens from 20 patients with multiple sclero is in the Baltimore Washington D C area Of 40 guinea pigs inoculated with cerebrospinal fluid from these patients none showed evidence of brucellosis Cultures of 11 cerebrospinal fluid specimens were negative and negative reactions to agglutination for brucella were found in the 6 specimens so tested If the minimal requirement for a skin reaction is 0 5 cm of edema at the inoculation site in 48 hours only one of these patients had a brucellergin reaction and three had reactions to the suspension of killed brucella cells With less critical standards if erythema without edema is interpreted as a positive reaction 10 of the 20 patients with multiple sclerosis had a reaction and 13 of 20 controls with diseases other than multiple sclerosis had reactions to the brucellergin and 5 to the brucella suspension

(7) J A M A 143 1470 1474 A g 26 1950

was followed by rapid improvement which in 11 continued to complete remission Improvement in two others though definite was not as complete and the acute illness reappeared promptly when therapy was discontinued In six other patients relapse occurred one to eight weeks after cessation of therapy The two patients with incomplete remissions recovered promptly when re treated with chloramphenicol as did the one patient with a relapsing infection who received a second course of the drug

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(6) J A M A 144 519 524 Oct 14 1950

vealed a mixed infection of Staphylococcu aureus a diplococcus and many gram negative slightly curved rods with irregular staining properties that proved to be M mallei He was treated with vaccin and made satisfactory progress (Fig 6)

Mendelson knows of no specific treatment for glanders



Fg 5 (l ft) —Gl d n y th 15
Fg 6 (ght) —Jmp m t ft th py
(C t y f M d l R W U S A m d F es M J l 781 784 J ly 1950)

and believes prognosis to be poor Vaccine treatment in this patient appeared to be of value but caution must be used in pronouncing a cure as latency is characteristic

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PLAGUE

Plague Vernon B Link[9] (San Francisco) emphasizes the inevitability of sporadic cases of plague caused by association with infected wild animals Five cases were reported in New Mexico and eight suspected cases in California Montana Nevada New Mexico Texas and Utah from July 1949 through July 1950

During the past 50 years epidemics of human plague to

(9) J A M A 144 375 377 S pt 30 1950

Thus no statistically significant difference was observed in the skin sensitivity to brucella antigens of 20 patients with multiple sclerosis and 20 with other diseases There is also no greater correlation between the geographic distribution of multiple sclerosis and bovine brucellosis than between that of rheumatic fever of Schick positive reactors and multiple sclerosis mortality The evidence fails to support the previously suggested impression of a strong and consistent relation between brucellosis and multiple sclerosis

[A rather devastating follow up on the previous report (1949 YEAR BOOK OF MEDICINE p 60) —Ed]

GLANDERS

Glanders, an acute infectious disease of equines caused by Malleomyces mallei is characterized by ulcerating granulomatous lesions of the skin subcutaneous tissues and mucous membranes In man it is frequently fatal and often difficult to diagnose The protean manifestations in both the acute and chronic stages may suggest a number of clinical conditions and valuable time may be lost for protecting contacts if a case is undiagnosed Positive diagnosis cannot be made on clinical observations alone History of contact with horses mules or donkeys is highly suggestive in a patient exhibiting an ulcerative granulomatous lesion particularly of the nose Because of the virulence of the organism meticulous bacteriologic technic is essential

Ralph W Mendelson[8] (M C U S A F) reports four cases The patients had chronic lesions and had been in contact with horses or donkeys Diagnosis was confirmed bacteriologically Case 2 follows

Youth 15 first had infection in the left eye followed by mucopurulent nasal discharge ulceration of the nose and lip (Fig 5) irritation of the throat and some difficulty in swallowing The right eye became infected about six months before examination At no time were constitutional symptoms severe Examination revealed moderate corneal ulceration of the right eye with extensive conjunctival inflammatory reaction and moderate discharge The left eye was more extensively involved with complete loss of vision Bacteriologic examination of secretions from eye nose and skin lesions re

(8) U S Armed Forces M J 1 781 84 July 1950

TETANUS

Tetanus Immunization Ten Year Study Although many reports have been made on the immediate effectiveness of this procedure there have been few on longer term immunity levels John A Bigler[1] (Children s Memorial Hosp Chicago) states that the commonly accepted protective level of tetanus antitoxin in the blood is 0 01-0 1 unit of antitoxin/cc. blood serum Between 1938 and 1940 262 children were immunized with alum precipitated tetanus toxoid and combined tetanus and diphtheria toxoid plain or alum precipitated in doses of 0 5 or 1 cc Some children received two and others three injections for their basic immunization Many have received one or more booster injections during the intervening 10 years Titrations of the blood serum of these patients for tetanus antitoxin totaled 1 363 Ages at the time of primary inoculation varied from 6 months to 12 years

Detectable amounts of tetanus antitoxin were present in the serum of all immunized children tested up to 10 years after immunization Adequate basic immunization was achieved with either two or three injections but protective levels were not always obtained with two injections When two injections are used a booster injection should always be given after an injury no matter how short the interval When three injections are given the third one acts like a booster injection The stimulation of a booster injection was adequate up to nine years after primary immunization and would undoubtedly be just as effective for many more years An adequate response was obtainable from as many as five booster injections in the same child Response to the booster injections was rapid occurring within the first seven days

From this study it appears that the more injections given the longer the antitoxin titers remain above 0 1-0 2 units After two injection immunization many titers decrease below this level after 1 month after three injections such levels are reached only after 3-6 months and after four injections only after 6-12 months It would seem advisable to give a booster injection to an immunized person at the time of an injury from which tetanus might develop

(1) A M A Am J Dis Child 81 226-32 February 1951

taking over 400 cases have taken place in California Washington Louisiana Texas and Florida all but one during epizootics in domestic rodents particularly among rats Plague infected wild animals have been found in over half the counties of New Mexico and plague was present in 11 counties in 1949 when five human cases resulted from contact with wild rodents the probable sources being pocket gophers squirrels cottontail rabbits and in two cases prairie dogs

Diagnosis of human plague is suggested by the clinical picture supported by the epidemiologic situation and confirmed by laboratory determinations In the presence of axillary or inguinal lymphadenopathy plague should be considered in differential diagnosis Plague must be differentiated from adenitis due to tularemia streptococcic and staphylococcic infections lymphogranuloma venereum syphilis and filariasis *Septicemic plague must be differentiated from* tularemia typhus typhoid malaria and the commoner causes of septicemia Pneumonic plague must be differentiated from other types of pneumonic involvement Diagnosis of plague can be confirmed by aspirating the bubo to make smears cultures and animal inoculations In septicemic cases blood cultures are easily obtained in the pneumonic type the sputum is loaded with plague bacilli

Treatment with streptomycin and sulfadiazine is the preferred method Penicillin was the first therapeutic measure in *the New Mexico cases In the two fatal cases it was the only* drug used and the true diagnosis was not suspected until after death Penicillin has no value in human plague Streptomycin and sulfadiazine should be given immediately whenever axillary or inguinal lymphadenopathy is present and even when there is only a possibility that the disease is plague Unless plague is suspected diagnosed and treated early eventually a case occurs in which a pulmonary infection develops and initiates a pneumonic outbreak with a far more serious loss of life than that resulting from the sporadic appearance of single bubonic cases

three months in doses of 0 03 0 05 units in adults and com bined with disulon* If there is a spinal block the cisternal route should be used if the cerebrospinal fluid is under ab normal pressure due to a block at the base the intraventricular route should be used if the block is in the optochiasmic re gion injection should be suborbital

By means of this program the incidence of delayed death was reduced from 27 9 to 16 6 per cent and the authors hope to achieve a further reduction

[We do not see as much tuberculous meningitis in this country as clinicians do in some other parts of the world The impressive th ng about this and the succeeding articles is the stress on prolonged energetic courageous treatment Too often there is a tendency to lo e hope when a block occurs —Ed]

Streptomycin Treatment of Tuberculous Meningitis in Children E Lorenz[3] (Univ of Graz) treated 33 children with streptomycin sometimes combined with sulfonamides Mortality for 19 under age 4 was 63 per cent for 10 aged 5 10 50 per cent and for 4 aged 11 15 zero The younger patients had severe complications These figures though not statistically significant suggest that older children have a bet ter chance of recovery Early diagnosis is important When *treatment followed onset of the disease by only one week* mortality was 43 per cent when the interval was two weeks *the rate rose to 50 per cent and when three weeks elapsed it* was 75 per cent

Streptomycin must be given uninterruptedly over a long period and administered into the lumbar spine as well as into the muscle For intramuscular injection dosage is 20-30 mg/kg body weight daily in two doses For intralumbar injection it is 1 1 5 mg/kg body weight given daily for three months then every other day twice a week and finally once a week Suboccipital and intraventricular injections do not appear necessary if the drug is injected intraspinally

Two of the 33 children had serious complications due to intolerance to streptomycin A boy 13 after intralumbar in jection had vomiting spasms of arms and legs mydriasis and anisocoria and tendon reflexes disappeared Symptoms cleared during the day Another boy 9 had violent vomiting rapid feeble pulse dilated pupils nystagmus and delayed pupillary reaction to light which disappeared on the third day

(3) W n kl W b b 62 417 420 J 1950

TUBERCULOUS MENINGITIS

Delayed Deaths in Tuberculous Meningitis Treated with Streptomycin and Their Prevention are discussed by Fd Ben hamou F Destaing P Viallet E Albou and M Timsit[2] (Al giers) who stress the importance of early diagnosis and rapid far reaching treatment based on observations in 172 cases

The typical clinical picture is presented by a patient who seems to be getting well for a few months the antibiotic has had a favorable effect and rapid recovery is expected when suddenly signs indicate a serious turn and death follows ex acerbation of all symptoms

CASE 1—Man 29 seemed to have recovered from tuberculous meningitis Examination showed progressive improvement tubercle bacilli in the cerebrospinal fluid were reduced and temperature was normal Suddenly he had a violent headache and high fever lumbar puncture showed 119 cells/cu mm and 0 4 Gm albumin In eight hours he became comatose and died

CASE 2—Girl 7 had recurrence of fever in the seventh month of illness after a period of satisfactory improvement with lowered temperature and weight gain Streptomycin was given again but she became hyperpyretic and increasingly somnolent rousing only for nourishment and died at the end of the eighth month

CASE 3—Man 24 had flaccid paraplegia and sphincter disturb ances two months after onset of meningitis Ocular fundi showed papillitis Laminectomy in the seventh month disclosed spinal mar row encased in a weblike sheath and cerebrospinal fluid blocked at that point He died after prolonged hyperpyrexia

CASE 4—Man 30 had pulmonary tuberculosis with symptoms of meningitis which improved after three months streptomycin therapy Cytology showed progressive decline in tubercle bacilli He grew weaker and died in the fifth month of illness

Of the new tests used in tuberculous meningitis (en cephalography electroencephalography arteriography and electrophoresis) air injection is the best for the fluid in the ventricle can be examined and intracranial lesions clearly re vealed by x ray

In some cases of tuberculous meningitis treatment is fu tile in others immediately after diagnosis antibiotics should be injected as near the site of the lesion as possible If the cerebrospinal fluid circulates freely streptomycin should be given by lumbar injection daily or twice daily for two or

(2) Pr sse méd. 58 1058 1061 O tobe 1950

period 3 accurate evaluation of the circulation of cereb spinal fluid and determination of the diffusion index led combination of intracisternal with intrathecal streptomy therapy when necessary In period 4 intraventricular and s dural streptomycin therapy was initiated in patients w supratentorial block

The percentage of recovery was high More than 100 tients had normal cerebrospinal fluid without residua in

RESULTS OF THERAPY IN 265 CASES OF TUBERCULOUS MENINGITIS

T M P R	D	P TS D d	L g	C d	D H or
1	Dec 1946 June 1947	44	13	10	/7
2	July Dec 1947	35	31	29	5J
3	Jan June 1948	20	40	32	33
4	July Dec. 1948	6	34	78	15
5	Jan June 1949	8	34	5	19

central nervous system Some had been well for more th two years Among those who recovered there was only c relapse four months after cerebrospinal fluid became negati

Tuberculous Meningitis Results of treatment of tuber lous meningitis with streptomycin have suggested the need newer methods of chemotherapy Hugh Cairns Honor Smith and R L Vollum (Oxford England) believing tl this conclusion is premature describe their results with stre tomycin alone and supplemented with intrathecal injectic of tuberculin Since November 1946 they have treated 93 p tients with tuberculous meningitis In the first 60 who h been treated for more than a year recovery rate was 50 p *cent another 6 or 8 patients might have survived with mc* acute diagnosis more persistent streptomycin therapy or mc prolonged hospital care Most deaths occurred in the fi three months relapse rate after a full course of treatment w low (4 of 60) Each patient was given streptomycin intr thecally for the first 6 12 weeks or even longer (adults 1 mg children 50 75 mg daily) and streptomycin intramusc larly without rest periods for not less than 6 months (adu 2 Gm children 20 mg/lb daily) As judged by psychometi tests and performance at work or school for as long as 2 years the quality of intellectual recovery was satisfactory

(5) J A M A 144 9 96 Sept 9 1950

Repeated hearing and equilibrium tests showed no reduced acuity The caloric test showed variable reduction in reflex stimulation only 13 3 per cent of children reacting normally In three children obesity developed slowly and was unrelated to nutritional intake or prolonged bed rest Two children had character changes with definite signs of moral insanity which slowly receded in three or four months

Results of Therapy in 265 Cases of Tuberculous Meningitis are reported by Arrigo Galeotti Flori[4] (Florence, Italy) Koch s bacillus was demonstrated in the cerebrospinal fluid in all patients

TECHNIC—Streptomycin was given intrathecally—20 25 mg for infants 30 50 mg for children and 50 70 mg for adults—daily for 40 60 and 80 days respectively In severe cases for the first few days intracisternal injection was also done After the treatment period lumbar punctures were done on alternate days for several weeks and as the cerebrospinal fluid gradually returned almost to normal were decreased to three then two and finally one a week until the colloidal gold reaction (Lange s) became negative If supratentorial block was diagnosed trephining was done immediately Streptomycin was carried to the ventricles and subdural spaces by plastic tubing inserted in burr holes Streptomycin—200 300 mg in infants 300 500 mg in children and 500 600 mg /24 hours in adults —administered intramuscularly in two or three separate injections was continued for a few weeks after complete recovery Sulfone 50 100 mg /kg /day was administered intravenously for the duration of the disease with only brief monthly omission periods Paraaminosalicylic acid was generally used only in chronic cases in which streptomycin therapy had been continued for several months The sodium salt 0 5 0 8 Gm /kg /24 hr in 5 per cent solution was administered intravenously by drip and intrathecally in the same dosage as streptomycin

Results of treatment are summarized in the table Patients were considered cured if the cerebrospinal fluid was normal those listed under the heading living were clinically well but still had slightly elevated cerebrospinal fluid protein levels and positive Lange s reactions In time period 1 intrathecal therapy was discontinued early with consequent relapses in some instances rendering the disease chronic and leading to blocking and hydrocephalus Streptomycin and sulfone dosage and other supportive measures were the same throughout all time intervals Prolonged intrathecal treatment initiated in period 2 lasted until the cerebrospinal fluid was normal In

(4) Pediat 6 391 395 September 1950

During the first weeks of streptomycin treatment there were usually frequent bursts of pleocytosis with white cell counts above the range seen in untreated disease Typically these high spikes of cells contained 60 80 per cent polymorphonuclear leukocytes They were not due to subarachnoid bleeding from lumbar puncture pyogenic infection or irritation by intrathecally given streptomycin since they disappeared before intrathecal injections were stopped and did not reappear when these were resumed These spikes of cells and protein in the cerebrospinal fluid are not seen in other varieties of meningitis treated by streptomycin but seem specific for tuberculous meningitis Since they might have been caused by liberation of bacterial breakdown products i e of tuberculin into the cerebrospinal fluid of the sensitized patient PPD was administered intrathecally in three patients in whom hope of recovery had been abandoned

CASE 1—Boy 2 with miliary tuberculosis being treated with streptomycin in the third month of proved meningitis was severely wasted with progressive hydrocephalus and intense head retraction and in coma. The extremities were spastic immobile and tightly flexed The pupils were dilated and fixed to light and he appeared blind He had complete spinal block Injections of PPD first into the lateral ventricle and then the cisterna magna resulted in improvement Ten months later he was a fat active healthy looking little boy with a head of normal size a growing vocabulary and what appeared to be normal intelligence There was still slight and diminishing residuum of right hemiparesis Chest x rays were clear cerebrospinal fluid was normal and the spinal theca open

Results in other patients confirmed previous experience that satisfactory recovery does not follow once decerebrate rigidity has been established but proved that intrathecal injection of PPD dissolves the exudate as Koch claimed for his tuberculin in 1890 His use of tuberculin however was followed by severe dissemination of the disease whereas under cover of streptomycin this complication can be prevented Intrathecal use of tuberculin is being cautiously extended to a larger series of patients Frontal burr holes are advised for ventricular taps should the reactions to injections be too intense (after each injection of PPD there was a temporary and sometimes alarming exacerbation of meningeal symptoms with rise of intracranial pressure) In the presence of active meningitis intrathecal injections of PPD are potentially extremely dangerous Without exceedingly careful grading of

all cases Physical disabilities in the 30 survivors are total deafness in 2 fits in 1 who had epilepsy before meningitis slight weakness of one hand as the remains of hemiparesis in 2 and somatic tuberculosis requiring treatment in 4

With this regimen results in cases of meningitis associated with miliary tuberculosis or pulmonary tuberculosis of adult type were bad Hence it was decided to treat these patients with streptomycin intramuscularly daily for 12 months and with three or four courses of streptomycin intrathecally during the same period Results justified this unusually prolonged treatment

Indications of active disease such as third nerve palsy and hemiplegia appeared up to 17 weeks after beginning of treatment In patients who subsequently recovered Mycobacterium tuberculosis grown from the cerebrospinal fluid in the eleventh week of treatment was seen in films of the cerebrospinal fluid in the seventeenth week

Despite great care with daily lumbar punctures the spinal subarachnoid space became partly or completely blocked at some stage of the illness in about a third of patients Bifrontal burr holes were immediately made and streptomycin was injected into the ventricles or occasionally into the cisterna magna until the lumbar subarachnoid space opened again Free access to the cerebrospinal pathways should always be maintained either for giving streptomycin or withdrawing cerebrospinal fluid to relieve rise of intracranial pressure Frontal burr holes are advised at the outset of treatment

In a few patients after sharp onset of tuberculous meningitis symptoms may remit or remain deceptively mild for weeks or months Harm has been done by stopping streptomycin therapy prematurely in patients who ultimately were proved to have tuberculous meningitis but not by continuing intrathecal and intramuscular injections of streptomycin for as long as a month in patients in whom some other disease was ultimately demonstrated In miliary tuberculosis lumbar punctures should be done weekly because under systemic streptomycin treatment evolution of meningitis in such cases may for weeks be almost asymptomatic In a few cases the meningitis may be of the serous variety but a few weeks of treatment with streptomycin intrathecally will not harm these patients

Mycobacterium tuberculosis and leprae evidently possess common antigens which stimulate production of common agglutinins in human serums Striking immunologic response against antigenic components of the tubercle bacillus is elicited by infection with Hansen s disease Inability to grow M leprae has naturally hampered serologic studies of Hansen s disease The technic described can be useful in future studies of this entity

[Most workers have been disappointed in this test as a guide to clinical activity in tuberculosis Perhaps it will find a place in connection with leprosy —Ed]

Critical Review of Present Position of Sulfone Therapy in Leprosy is presented by R G Cochrane[7] (Christian Med College Vellore South India) Since the results of diaminodiphenylsulfone therapy are not greatly superior to and the drug is more toxic than sulphetrone given parenterally the latter has the advantage Recently oral administration of diaminophenylsulfone has been advocated because of freedom from serious toxic effects This claim needs serious consideration for it seems to obviate the need of injection and to reduce the cost of sulfones to a level which would make it possible for every lepromatous patient to take the drug There are however certain serious drawbacks to this form of therapy Great care must be taken to stabilize the patient to eliminate the possibility of toxic signs To ensure a patient s taking a daily dose of a drug over not months but years is difficult unless there is strict control over its administration This method therefore is not applicable in outpatient clinics where patients can come only once or twice a week Another disadvantage is the necessity for periodic courses of iron and yeast therapy to overcome the tendency to severe anemia In addition every regimen for oral administration that has been used has given toxic results in most cases

Owing to the high cost and relatively high toxicity of sulphetrone given orally experiments were conducted on the parenteral administration of an aqueous solution and of an oily emulsion In institutions not fully equipped for laboratory work or in outpatient centers where this is impossible aqueous sulphetrone seems to meet the need in cases in which it is desirable to administer a sulfone preparation Aqueous sulphetrone has no significant effect on the red cells and hemoglobin

(7) T R y Soc T p M d & Hyg 44 59 270 D mb 1950

dosage and close observation and supervision of the patient disaster may easily occur

[This is an excellent discussion of the whole problem. The use of tuberculin intrathecally is new and an exciting idea. The reactions to it are severe and doubtless dangerous; nevertheless the effect in the case cited seems miraculous. Further trial of the method by capable clinicians is warranted.—Ed.]

LEPROSY

Hemagglutination of Tuberculin Sensitized Sheep Cells in Hansen's Disease (Leprosy) The hemagglutination test of Middlebrook and Dubos provides a readily available laboratory tool for studying the serologic response of patients infected with tubercle bacilli. *Max Levine[6] (Honolulu)* used this technic in measuring serologic response in Hansen's disease. Specimens were obtained from 96 patients with tuberculosis and 105 with Hansen's disease (80 in the active phases of the disease all of whom were bacteriologically positive and 25 with arrested cases all of whom were bacteriologically negative). As may be seen from the table the low hemag

AGGLUTINATION OF TUBERCULIN SENSITIZED SHEEP RED CELLS

Agglutination Titer	Specimens %		Hansen's Disease Patients	
	96 Leahi T B Hosp Patients	40 Blood Bank Donors	80 Active (Bact Pos)	25 Released (Bact Neg)
Neg 1 4	11 5	75 0	1 3	24
1 4	11 5	15 0	8 7	32
1 8	11 5	7 5	13 7	16
1 16	28 1		17 5	16
1 32	14 6	2 5	11 3	4
1 64	17 7	—	17 5	—
1 128	5.2		11 3	8
1 256	—	—	8 7	
1 512	—	—	6.2	
1 1024			2 5	
1 2048		—	1.3	

Clinical status of a [illegible]

glutination titers of the 40 controls and the frequently high titers in patients with Hansen's disease who were bacteriologically positive stand out in strong contrast. The lower intermediate titers of bacteriologically negative patients with Hansen's disease in whom the disease was arrested are also striking.

(6) Proc Soc Exper Biol & Med 76 171 173 Jan 1951

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(7) T Roy Soc T p M d & Hyg 44 259 270 D mber 1950

content of blood and therefore periodic blood counts are unnecessary Furthermore its toxicity is low The only condition likely to interfere with treatment is allergic dermatitis There appear to be no other important toxic signs Another advantage is that the reaction potentialities of this drug are low However two reactions need mention With aqueous sulphetrone as with all sulfones reactions may take the form of acute iritis which may be alarming If vigorous atropine treatment is given and the pupil maintained at full dilation however vision will not be impaired and the reaction phase will pass Neuritis is also a sign of reaction but may also be a toxic phenomenon resulting from sulfone therapy Because of difficulty of and pain on injection an oily emulsion of sulphetrone is unsuitable for mass treatment

Diasone® and sulphetrone are in many ways alike When *given orally cyanosis anemia and severe occipital headache* may result Three other sulfone preparations should be mentioned Promin® has been used little because of its cost the necessity of daily intravenous injections and the serious anemia resulting from it Promacetin and sulfone cilag are both effective The first is given by mouth and therefore has all the drawbacks of daily oral therapy The second may be given by intravenous injection but subcutaneous injection is preferable

Sulfone therapy is indicated for all lepromatous patients If adequate laboratory facilities are available and the organization of the institution is efficient diaminophenylsulfone may be given orally (because of its low cost) if the precautions indicated are strictly followed In all other institutions 50 per cent aqueous sulphetrone *should be used Bacteriologic* improvement is slow When bacilli show beaded granular and acid fast dust forms it can be concluded that the patient is less infective but to assume that these forms are nonviable Mycobacterium leprae may prove a dangerous example of wishful thinking

Sulfone therapy promises to render an increasing proportion of patients negative and will in most cases prevent or alleviate the distressing eye and throat symptoms Blindness will therefore be averted and laryngeal stenosis prevented Specific therapy is not the only aspect of leprosy treatment to consider however for this new hope challenges the ortho

pedic surgeon and physiotherapist to devise measures which will as surely prevent deformity or correct it when present as the sulfone remedies prevent lepromatous leprosy from advancing

AMEBIASIS

Terramycin Treatment of Amebic Dysentery Preliminary Report Francisco Ruiz Sanchez Rebeca Riebeling and Carlos Arreola[8] (Univ of Guadalajara) report good results in 20 carriers of Endameba histolytica and 8 patients with vegetative forms of the parasite in the feces Carriers were given 25 100 mg terramycin/kg body weight daily and the patients received 30 50 mg/kg daily for four to six days Fresh fecal material was examined three to six times daily for 14 days samples from the ulcerated colon walls of the patients were also analyzed

The parasite disappeared from the feces of 19 of the carriers (from 15 within 24 hours of beginning therapy) and all the patients Terramycin seemed to favor growth of Giardia lamblia in the one patient in whom it too had been present before treatment To prove the validity of these results the study must be extended over a longer period and under more rigid conditions

[Terramycin seems to be superior to the other antibiotics in amebiasis —Ed]

HISTOPLASMOSIS

Treatment of Disseminated Histoplasmosis with Ethyl Vanillate In 1948 ethyl vanillate a fungicidal compound the ethyl ester of vanillic acid was developed Initial studies revealed that growth of Histoplasmosis capsulatum was inhibited by ethyl vanillate in concentrations of 20 mg/100 cc. in plasma fortified mediums incubated at 37 C A method of quantitative analysis of ethyl vanillate in blood serum and body tissues was then developed

Although present data are inadequate in determining the safety or value of ethyl vanillate in treatment of fungous infections the well recognized serious course of progressive dis

(8) M d i a Mé ico 30 365 369 S pt 10 1950

seminated infections with H capsulatum influenced Amos Christie James G Middleton J Cyril Peterson and David L McVickar[9] (Vanderbilt Univ) to use the drug in 12 consecutive cases of culturally proved histoplasmosis representative of the progressive disseminated form Previous experience with 35 cases of the progressive type enabled the authors to separate the progressive cases from those in which there was a milder degree of infection Of the 12 patients treated 5 survived and were well when last seen although 1 or 2 might have survived without specific therapy it is inconceivable that all could have They probably would have died in a few weeks or months if untreated

Ethyl vanillate a solid with a pungent phenolic odor causes a burning sensation in the mucous membranes of the mouth The necessity of administering the drug in multiple gram doses every four to six hours presents a problem Capsules or covered pellets may be given to adults but with infants the only feasible method is to administer a solution The drug is soluble in olive oil a 40 per cent solution was found to be the most practical preparation It had to be given by gavage at intervals coinciding with feedings From present limited experience it seems best to start with small doses and increase to higher levels gradually to avoid high blood levels In infants without diarrhea 1 5 Gm /kg /day divided into four to six doses the upper limit of the dose usually provides blood levels of 20 30 mg /100 cc It is suggested that initial dosage be 0 5 Gm /kg /day in divided doses increased in steps of 0 5 Gm every five to six days until dosage of 1 5 Gm/kg /day *or desired blood level is attained In adults smaller* doses should be used probably less than 50 per cent of the dose used in infants as calculated on a weight basis A better basis for calculating the adult dose would be to relate it to the surface area The doses given by the authors are equivalent to about 5 Gm /sq m body surface/24 hr for maximal dosage The narrow margin between doses required to give therapeutic levels and those producing toxic manifestations makes it imperative to have adequate laboratory controls when this drug is used

All infants showed slight drowsiness apathy and inactivity persisting in some degree throughout the treatment period

(9) Ped atri s 7 7 18 J a y 1951

but recovered completely when the drug was stopped Three patients had sudamenous rashes which may have been due to excessive perspiration In one patient at the end of the course fever presumably due to the drug disappeared as soon as the drug was stopped Two patients on moderately high doses and with moderately high levels of the drug had respiratory alka losis with symptoms imilar to those of salicylate poisoning Several other infants had some degree of hyperpnea at some time during treatment a high and perhaps toxic level (56 mg/100 cc) developed in one early in treatment Autopsy showed necrosis of hepatic cells around the central veins and degenerative change in the proximal convoluted renal tubules lesions not seen in progres ive histoplasmosis These may have been due to the drug and may explain the failure in that case since the high and perhaps toxic level produced a sociated changes which would not allow the tissue to me tabolize the drug to its effective end products or conjugates

Ethyl vanillate is the only known effective therapeutic agent for disseminated and progre sive histoplasmosis The margin between effective therapeutic levels and those which produce toxic manifestations is only about 25 30 per cent a margin of safety too small for a desirable therapeutic agent However the grave prognosis of progressive disseminated histoplasmosis seems to justify use of any agent which offers some hope of therapeutic effectiveness and which does not regularly produce severe toxicity

[*Not perfect but the best agent yet reported for histoplasmosis —Ed*]

RELAPSING FEVER

Tick Borne Relapsing Fever at the Witwatersrand Gold Mines Treatment with Aureomycin Of 300 000 native labor ers examined annually at the central hospital of the Wit watersrand Native Labor Association roughly a third are from areas outside the Union of South Africa mainly Por tuguese East Africa One of the frequently encountered dis eases is tick borne relapsing fever which occurs sporadically in the Union but is endemic in many other parts of southern Africa Symptoms and signs include headache with fever (101 103 F) pulse rate of 90 110 and splenic enlargement of

2 3 fingerbreadths below the costal margin Epistaxis occurs in about 50 per cent of cases Diagnosis is made from blood smears taken during the pyrexial period and stained with Leishman s or Giemsa s stain The spirochete is easily recog nized

No reports have been published on the effect of aureomy cin on Spirochaeta duttoni Because aureomycin is effective against certain other spirochetes and because no satisfactory treatment has been found for tick borne relapsing fever R M Yeo[1] (Johannesburg) gave this antibiotic to 25 patients Dose was 2 capsules (0 5 Gm) initially followed by 1 capsule every 4 hours until temperature was normal for 12 hours Average total dosage was only 12 capsules Dosage was low because of the short pyrexial period difficulty in obtaining supplies and expense of the drug

A favorable reaction was obtained Temperature which was around 103 F when treatment was begun fell rapidly by crisis accompanied by profuse sweating and was usually normal in 24 hours The average pyrexial period for untreated patients was 48 hours and temperature fell by lysis With fall in temperature symptoms rapidly diminished Only 3 of the 25 patients relapsed during the three weeks after treatment

Despite the small number of patients treated and the small dosage given results suggest that aureomycin has a spiro cheticidal effect on S duttoni A more concentrated course of treatment with larger dosage of the drug would likely eliminate the spirochetes

[The good clinical results with aureomycin are in agreement with results of tests on experimental animals As things stand today aureomy cin seems the drug of choice —Ed.]

RICKETTSIALPOX

Treatment of Rickettsialpox with Aureomycin Early studies of aureomycin indicated that this antibiotic had not only a wide range of antibacterial activity but also remarkable antirickettsial properties Harry M Rose Yale Kneeland Jr and Count Dillon Gibson[2] (New York City) report results of aureomycin therapy in eight patients with rickettsialpox the

(1) So th Af n M J 24 457 459 J e 1950
(2) Am J M d 9 300 307 S ptembe 1950

one type of human rickettsial disease in which the therapeutic effect of aureomycin has not been definitely established Usual dosage was 2-4 Gm daily given orally

The acute febrile stage of rickettsialpox usually lasts about one week fever and associated symptoms abating gradually over the final two or three days of illness Only rarely do the acute manifestations of the disease subside as soon or as quickly as they did in each of these patients after aureomycin therapy (usually within 24 hours) The uniformly rapid and favorable therapeutic response was evidently not a chance observation even though only eight patients were treated Rickettsialpox probably may be added to the list of rickettsial infections in which aureomycin has a prompt curative effect

In three of the patients no specific antibody response was detected by the complement fixation test during convalescence Nevertheless the characteristic clinical picture and recovery of rickettsias from blood taken in the acute phase confirmed the diagnosis In more than 40 untreated convalescent rickettsialpox patients the authors invariably found significantly elevated antibody titers by the same serologic method using antigen prepared from the same strain of Rickettsia akari Aureomycin was probably the responsible factor and may have suppressed rickettsial multiplication so promptly and completely that the resulting antigenic stimulus was insufficient for detectable antibody production

Rickettsialpox Report of Serologically Proved Case Occurring in Resident of Boston George Pike Sidney Cohen and Edward S Murray[3] (Harvard Univ) report a case clinically and serologically characteristic of rickettsialpox in a patient who had lived in Boston continuously for five months before illness

Woman 56 had headache and tenderness of the lymph nodes behind the right ear followed in two days by malai e chilly sensations drowsine s and temperature of 102 F There were several moderately enlarged tender lymph nodes in the right posterior cervical chain and one in the right supraclavicular region Scattered over the arms legs and trunk were about 12 maculopapules with small gray white opaque vesicles at the apex of 2 The next day the rash was much more extensive The individual lesion 5 8 mm in diameter was a small papule in the center of an erythematous base

Drowsiness headache malaise and fever persisted with slight

(3) N w E gl d J M d 243 913 915 D 7 1950

increase in skin lesions until nine days after onset of the first symptoms when definite subsidence of symptoms and fading of the rash were noted The only medication was a few aspirin tablets Serum specimens taken during the acute illness and convalescence and studied for Proteus OX agglutinins and complement fixing antibodies to epidemic typhus murine typhus Q fever Rocky Mountain spotted fever and rickettsialpox showed a diagnostic rise in titer with the antigens of rickettsialpox and Rocky Mountain spotted fever

Diagnosis of rickettsialpox is confirmed by development in convalescence of a high titer of complement fixing antibodies in tests with the antigens of Rickettsia akari Simultaneous occurrence of complement fixation with Rocky Mountain spotted fever antigen is a cross reaction regularly obtained in serums in rickettsialpox The negative or very slightly positive Weil Felix reaction with P OX 19 in this patient is the rule in rickettsialpox Rocky Mountain spotted fever on the other hand usually produces a distinctly elevated agglutinin titer for P OX 19 or OX 2 Rickettsia akari was definitely isolated from mice trapped in the patient s place of employment

In diagnosis of rickettsialpox chickenpox smallpox Rocky Mountain spotted fever and typhus fever must be differentiated Rickettsialpox is most commonly confused with chickenpox but differentiation is not difficult

[We should be on the lookout for this disease in other parts of the country —Ed]

Q FEVER

Q Fever in Wool and Hair Processing Plant is reported by M Michael Sigel T F McNair Scott Werner Henle and A Henry Janton[4] (Philadelphia) The outbreak was recognized when a worker was hospitalized in February 1948 with chills fever headache cough and pain in the back and left chest Q fever was diagnosed after routine serum tests for viral and rickettsial pneumonia

During the first three months of 1948 about 30 employees had been absent because of a respiratory illness generally called flu or grippe Blood samples were taken from 152 of 186 employees and serums tested with the antigen of Q fever

(4) Am J P b He lth 40 524 532 May 1950

Sixty seven gave positive reactions ranging in titer from 1 2 to 1 2048 39 had titers of 1 64 or higher This indirect evidence that many employees had had contact with Coxiella burneti combined with the observations in the first case suggested that the outbreak was due to the rickettsia of Q fever

Clinical data were incomplete but in general the illness was mild and the workers believed they had colds or flu Only two workers were hospitalized and a few seen by physicians Fever sweats chills and malaise were the commonest symptoms and illness lasted about 14 days

This outbreak of Q fever was apparently due to inhalation of C burneti by workers handling raw wool and goat hair presumably containing dried ticks or tick feces in a dusty atmosphere Recognition of this outbreak through routine testing of serum specimens from one patient with upper respiratory illness indicates the importance of testing with the several viral and rickettsial antigens serums from patients with pneumonia or undifferentiated infection of the upper respiratory tract Tests with the Q fever antigen are especially important when the patient has had contact with raw wool meat or milk or with sheep goats or cattle Q fever should be recognized as an occupational hazard It has occurred among stock handlers and packing house and wool workers and has been transmitted to consumers by milk

Q Fever in California Recovery of Coxiella burneti from Naturally Infected Air Borne Dust The mode of transmission of Q fever to man is not clear although studies of laboratory outbreaks of Q fever suggest that air borne transmission or dissemination of the rickettsias was involved In the Italian outbreaks contaminated dust may have been the source of infection and may explain occurrence of Q fever in some outbreaks as a place disease In California C burneti is shed in the milk of infected dairy cattle sheep and goats However use of raw milk or contact with dairy cattle sheep or goats does not account for many human cases Therefore infection may possibly arise from air borne dust originating in environments contaminated with body secretions or excreta of infected livestock

Paul D DeLay (Sacramento Calif) Edwin H Lennette and Kenneth B DeOme[5] (Berkeley Calif) collected air sam

(5) J Immunol 65 211 2 9 August 1950

ples in broth from a dairy, sheep ranch and goatery where human and animal Q fever infections were known to have occurred and inoculated guinea pigs Results showed that on premises harboring infected domestic livestock C burneti may be present in the dust laden air The possibilities thus exist that human or animal infection may be acquired by exposure to contaminated air and that air borne dissemination of rickettsias might explain some outbreaks and sporadic cases of Q fever which have occurred in absence of known direct contact with domestic livestock

Q Fever Transmission from One Human Being to Others, Report of Three Cases is made by David L Deutsch and E Taylor Peterson[6] (Veterans Admin Center Los Angeles) It has been stated that Q fever is rarely if ever transmitted from one human being to another That human to human transmission is possible was suggested by recent observation of a patient acutely ill with Q fever and the subsequent appearance of the disease in 14-23 days in three persons who attended him They had symptoms clinically compatible with Q fever and serologic tests positive for the disease None of the personnel resided near a dairy had contact with livestock or ingested raw milk however they did handle the patient s bed linen clothes bedpans and food trays and had personal contact with him Mode of transmission was not determined

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BRILL S DISEASE

Brill's Disease Clinical and Laboratory Diagnosis During an epidemic of typhoid in 1896 Brill observed sporadic cases of an atypical typhoid like disease in which the Widal reactions were negative In 1910 he reported on 255 such cases all having several characteristics in common the disease usually occurred in Russian or Polish immigrants there was no infectiousness headache fever and malaise were prominent symptoms the most characteristic feature was a maculopapular rash beginning the fifth or sixth day and Widal reactions and blood cultures were negative

By 1932 it was established that there were two distinct

(6) J A M A 143 348 350 May 27 1950

varieties of typhus (1) caused by Rickettsia prowazeki the epidemic Old World variety spread from man to man by the body louse and (2) caused by R mooseri the murine variety spread from rat to rat by the rat louse and rat flea and occasionally transmitted from rat to man by the rat flea However since Brill s disease could not be attributed either to lice or to rat fleas this differentiation did not establish the position of Brill s disease as being clearly one form or the other

In 1934 Zinsser reviewed 538 reported cases of Brill s disease Over 94 per cent of the patients had come to the United States from areas of Eastern and Southeastern Europe where typhus had often occurred in epidemics Over 90 per cent were Jewish No connection could be traced between patients there was no observable domiciliary or occupational relationship Zinsser succeeded in isolating three strains of typhus rickettsias from patients with Brill s disease They failed to persist in mice thus resembling classic epidemic strains From these data Zinsser proposed that Brill s disease represents a recrudescence of an old typhus infection originally acquired in Europe implying that the rickettsias once acquired remain latent for many years in the tissues of infected human beings Cases of Brill s disease when occurring in louse infested communities might become foci of outbreaks of epidemic typhus Thus man might be the reservoir for epidemic typhus rickettsias

Edward S Murray George Baehr Gregory Shwartzman Robert A Mandelbaum Norman Rosenthal Joseph C Doane Laurence B Weiss Sidney Cohen and John C Snyder[7] undertook the present study to obtain new strains of the etiologic agent of Brill s disease to characterize them and to determine whether human body lice became typhus infected by feeding on patients with Brill s disease Studies were conducted in five hospitals serving communities with large numbers of foreign born Jews Whenever a patient was thought to have Brill s disease an attempt was made to isolate the etiologic agent by louse feeding and inoculation of animals with the patient s blood Criteria for tentative diagnosis were (1) fever of unknown origin occurring in a (2) foreign born person who had once lived in an area where typhus occurs in

(7) J A M A 142 1059 1066 Ap 8 1950

epidemic form and who complained of (3) intense persistent headache and had a (4) macular or maculopapular rash on the 4th to 6th day of the disease

The authors report on 14 patients who had Brill s dis ease established by both clinical and serologic evidence Typhus rickettsias were isolated from each of the seven pa tients studied on the 5th to 8th day of illness but all isola tion attempts on the seven patients studied between the 9th and the 12th day of illness were unsuccessful The following observations are confined largely to patients from whom rick ettsias were isolated

Age at onset ranged from 20 to 72 All patients were for eign born Jews Six patients had had a typhus like illness in Europe In four patients onset was sudden in three it was gradual over a day or two with short intervals of well being interspersed among episodes of chills feverishness malaise and headache Headache was the most constant distinguishing symptom Rash was present in all beginning the 4th to 6th day of illness Earliest manifestations were faint discrete macules or maculopapules 1 10 mm diameter and fading readily on pressure they first appeared on the anterior por tion of the chest then usually extended rapidly to involve most of the trunk arms and thighs Temperatures varied greatly and reached as high as 105 F Four patients were definitely confused two apathetic and only one was mentally clear throughout The course in two patients given aureomycin suggested that this drug reduces the severity of Brill s dis ease

Routine laboratory tests were of little or no help in differ ential diagnosis White blood cell counts were normal or only slightly elevated All patients had elevated complement fixa tion titers higher against epidemic than murine antigen Se rums of four patients did not agglutinate Proteus OX 19 organisms at any time serums of most other patients aggluti nated in very low titer In most laboratories 1 160 is the low est titer generally agreed on as diagnostic on this basis only 3 of the 14 patients had a diagnostic agglutination titer on the Weil Felix test All seven strains of organisms isolated were clearly of the classic epidemic type

Brill s disease is generally considered a mild form of ty phus but this opinion probably is erroneous since six of

the seven patients from whom rickettsias were isolated were moderately or very severely ill However mortality is low

[Evidence such as this supports the postulate that certain intracellular parasites (viruses and rickettsias) may continue to parasitize the cells of an animal host for years after the initial invasion Such persistence of the micro-organism could provide the antigenic stimulus which accounts for lifelong immunity after an attack of measles or yellow fever —Ed.]

BORNHOLM DISEASE

Bornholm Disease is a benign illness occurring both epidemically and sporadically according to J H S Hopkins[8] Patients are usually febrile The disease is characterized by pain usually of muscular type and variable intensity felt typically in the thorax or abdomen on deep respiration coughing laughing or movement There is usually some abdominal tenderness particularly just below the costal margin and the xiphisternum There are no true signs of visceral involvement A coarse pleural rub may occur The disease is extremely variable in appearance and severity In a mild case only malaise and pain on deep respiration may be present whereas in other cases there may be crippling pain of sudden onset abdominal rigidity headache or vomiting

The importance of the disease lies not so much in itself as in its potential mimicry of other severer illnesses After becoming familiar with the syndrome Hopkins realized that he had previously seen but missed many cases Laparotomy was done on one of his patients another was observed for a long period because of suspected tuberculosis and another was given sulfonamides and penicillin unnecessarily Similar mistakes in diagnosis abound in the literature Differential diagnosis is not difficult if the disease is borne in mind When right sided abdominal pain is the presenting symptom a diagnosis of appendicitis is often considered however there is no typical onset of appendicitis and pain is worse on deep breathing a symptom which does not occur in appendicitis until peritonitis develops The disease can be distinguished from pleurisy by the more pronounced general myalgia and abdominal tenderness and lack of association between severity of pain and loudness of the pleural rub

(8) B M J 1 1230 1232 May 27 1950

Etiology of Epidemic Pleurodynia Study of Two Viruses Isolated from Typical Outbreak T H Weller J F Enders M Buckingham and J J Finn Jr[9] report that intracerebral inoculation of 1 day old mice with throat washings collected during an outbreak in 1947 in the Boston area resulted in isolation of four strains of virus Two studied in detail were shown to be similar in their pathogenic and immunologic properties Mice are completely susceptible during the first two days of life After intracerebral inoculation of 100 L D 50 the animals die in three to six days with characteristic lesions of the liver and often of the pancreas Specific neutralizing antibodies against the two viruses developed during the illness in each of the two patients from whom the viruses were isolated Likewise a rise in neutralizing antibodies for both agents was demonstrated in paired specimens of serum from five other patients with epidemic pleurodynia These findings indicate that the viruses are of human origin and played an etiologic role in the epidemic An antigenic relationship between these agents and a strain of the Coxsackie group of viruses previously isolated in a sporadic case with symptoms compatible with those of epidemic pleurodynia was established

Coxsackie Viruses and Bornholm Disease G M Findlay and Elsie M Howard[1] (London) report that symptoms of myalgia resembling those of Bornholm disease (also known as epidemic myalgia epidemic myositis epidemic pleurodynia epidemic pleurisy) occurred in laboratory personnel during investigations with Coxsackie virus 2 and were followed in a few days by appearance of positive complement fixing antibodies in the blood

After working with the Coxsackie virus for three months a woman employee noted pain over the lower left ribs which was worse on breathing and became severe on the second day of illness She did not have headache Temperature was 99 100 F During the third day she was afebrile and severity of the muscular pain gradually decreased On the evening of the second day when she had become afebrile blood was drawn and injected intraperitoneally into suckling mice They remained in good health A complement fixation test on this

(9) J Immu 1 65 337 346 Septembe 1950
(1) B t M J 1 1233 1236 May 27 1950

serum for immunity to Coxsackie virus gave a negative result but another test four days after onset of symptoms gave positive fixation with Coxsackie virus 2 the strain with which most work was being carried out

A volunteer whose serum on numerous occasions had given a negative complement fixation reaction to Coxsackie viruses was then given an intranasal injection of 0 5 ml 1 100 suspension of suckling mice infected with Coxsackie virus 2 in saline He had no symptoms until 46 hours later when sudden pain was felt in the intercostal spaces immediately below the point of the right scapula It was more intense on taking a deep breath or laughing On the evening of the first day of illness 12 hours after onset of pain temperature was 99 2 F The next morning it was subnormal and the pain had lessened *It continued for 48 hours and did not recur* There were no other symptoms Complement fixation reaction 24 hours after onset of symptoms was negative but 72 hours after onset *complement fixing antibodies were detected in the serum* they were present nine weeks later

Serum from patients with Bornholm disease contracted *in three different localities fixed complement with and neutralized* Coxsackie virus 2 whereas they showed no reaction with Coxsackie virus 1 or 3 or normal mouse antigen A virus *closely resembling Coxsackie virus 2* was isolated from the blood stools and nasal washings of a patient in whom typical symptoms of Bornholm disease had developed 52 hours previously *complement fixing antibodies for Coxsackie virus 2* were present in the blood In addition complement fixing antibodies against Coxsackie virus 1 were found in the blood of *adults who had recovered from Bornholm disease* contracted in two other localities

It appears that Coxsackie viruses 1 and 2 are widely distributed *in Great Britain* and that some epidemics of Bornholm disease in this country are associated with infection with Coxsackie virus 1 or 2 or closely allied viruses

[*Similar work and similar conclusions are reported by Weller and* associates of Harvard Univ (J Immunol 65 337 340 September 1950) The place of the Coxsackie group of viruses is still somewhat uncertain but these findings by good worker deserve careful consideration For a different *kind of disease also attributed to Coxsackie virus see the next* article —Ed]

HERPANGINA

Herpangina Etiologic Studies of a Specific Infectious Disease which occurred during the summer of 1950 in six children in a suburban community within the metropolitan area of Washington D C are reported by R J Huebner Roger M Cole Edward A Beeman Joseph A Bell and James H Peers (Nat l Inst of Health Bethesda Md) The first case appeared in a girl aged 5 After fever of abrupt onset she complained of headache and abdominal pain Rectal temperature was 102 8 F and she vomited once The second day she seemed improved and temperature did not exceed 100 F but she complained of sore throat A number of small ulcers were noted on the anterior pillars of the fauces The lesions and all other evidence of illness disappeared on the third day without antibiotic therapy During the successive 15 days similar illnesses appeared in five children living in three nearly adjacent households

The small punched out ulcers with grayish bases and surrounding red areolae were similar in all cases and represented the most characteristic sign of the disease One to 10 lesions were observed Leukocyte and differential counts of three patients were within normal limits for the age group (4-11 years) although one patient appears to have had relative lymphocytosis Chest x rays of four patients during convalescence showed no abnormalities

Bacteriologic studies on material from throat lesions of four patients showed no significant organisms Attempts to isolate virus in 3 or 4 day old suckling mice were successful in each case Stool specimens taken during the early stages of the illness and from the same patients 4 21 days later were also positive for virus Stool specimens of 277 persons collected during a routine community survey were negative

Although the newly isolated virus strain (H3) was successfully propagated in suckling mice all attempts to propagate it in adult mice guinea pigs and rabbits inoculated by various routes failed High neutralizing antibody levels were demonstrated in convalescent serums of the four patients

(2) J A M A 145 6 8-633 M r 3 1951

tested Since increases in neutralizing antibodies were not observed when these serums were tested against other virus strains the observed rises were regarded as specific

Despite the possible misleading inference that herpes simplex virus is responsible for this disease the term herpangina has much to recommend it This name was first suggested by Zahorsky in 1920 and possesses the virtue of having been applied to a single entity in an unmistakable manner Subsequent studies of herpangina in metropolitan Washington resulted in isolation of the same or similar viruses in 26 of 31 patients

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POLIOMYELITIS

Possibilities of Specific Prevention and Treatment of Poliomyelitis In a review of current literature on specific poliomyelitis control William McD Hammon[3] (Univ of California) was struck by the divergent opinions on the possibility and/or practicability of passive or active immunization or vaccination against poliomyelitis These divergent opinions indicated the need for an objective review of the problem

The possibility of passively protecting monkeys and mice by serum against an intracerebral challenge of virus has been repeatedly demonstrated Gamma globulin from pooled adult plasma appears to be the most effective and readily available agent

Before discussing the appropriateness of a human trial with gamma globulin certain pertinent basic immunologic problems need consideration Does antibody play a direct role in protecting man against clinical disease and does it present a barrier to invasion of the central nervous system tissue? There is much suggestive evidence that it does Would prophylactic serum completely prevent infection as in rubeola and thus only postpone infection until later when risk of paralysis may be greater? Would presence of a large number of artificially immunized persons in a community reduce dissemination of virus and postpone the age of infection for even the nonimmunized? From data available it appears that immunity in poliomyelitis unlike that in rubeola probably

(3) Ped t 6 696 705 N mb 1950

does not permanently or completely prevent reinfection and a temporary carrier state If immune serum does not completely prevent infection is it not possible that active immunity of a more permanent nature might be acquired during a period of passive protection if a person is meanwhile exposed to infection in an epidemic area? It appears possible that serum prophylaxis administered to children during a poliomyelitis epidemic probably would not entirely prevent poliomyelitis infection and the concomitant development of an active more durable immunity Neither would it necessarily arrest or deter spread of the virus in the community by greatly reducing the number of persons susceptible to infection and a carrier state The infection might be entirely inapparent or lead to mild nonparalytic disease or to some modification of an otherwise more severe outcome

In the light of data available and pending the possible development of a safe effective and not too costly vaccine for active immunization a well controlled experiment with gamma globulin would appear to be in order If protection occurs at all it cannot be counted on for over six weeks unless infection occurs and converts the protection to an active immunity One two or three injections in children up to age 10 or 12 during each epidemic season might prove to be a practical means of protection and it is a means which is now available depending only on collection of adequate amounts of adult blood for processing

Active immunization presents a much more complex problem Here the problems of multiple immunologic types and development of methods of inexpensive commercial scale production of virus (now available only at large cost in minute amounts) are encountered In addition there are the dangers of multiple inoculations of brain tissue the only present source of even moderately large supplies of virus Furthermore repeated injections must be given over many years probably annually for unless safe mutant strains of each type miraculously appear inactive (killed) virus must be used The objection that naturally acquired immunity will be prevented possibly need no longer be held if immunity does not entirely preclude natural infection

A disadvantage of active immunization is that many persons who would never become paralyzed would be given the

vaccine to prevent a very few from having the rare paralytic manifestations of this ordinarily benign infection The average annual experience with poliomyelitis over a recent 20 year period in four northeastern states in heavily infected areas is 37 reported cases/100 000 children in the 0 9 year age group Only about 25 per cent of reported cases in this age group are fatal or end in residual paralysis of any significance If vaccination is practiced annually about 11 000 children would have to be immunized to prevent the annual average occurrence of each single fatal case or case of permanent disability It appears therefore that such vaccination would represent a far greater effort expense and risk of accident to thousands to protect a single person than vaccination used for other diseases

There seems to be a good indication for field tests of gamma globulin This agent is immediately available for trial and from a theoretical immunologic standpoint appears much more practical to use than a vaccine

[This critical review and discussion is timely in view of the frequent statements in new papers some of them made by re ponsible persons indicating that an effective vaccine is about to be perfected —Ed]

Complement Fixation Test for Poliomyelitis Virus Jordi Casals and Peter K Olitsky[4] (Rockefeller Inst) adapted the MEF1 a Lansing type of poliomyelitis virus to infant mice and obtained a highly active strain with an LD_{50} titer in excess of that usually yielded by adult mice In the medium of newborn mouse brain and in such an increased titer the virus lends itself to preparation of a suitable antigen for specific and reproducible complement fixation

METHOD —The source material was brain and cord tissue from newborn mice infected intracerebrally with MEF1 virus Serial passages to 3 or 4 day old mice carried out every three or four days resulted in an adapted strain now in its 32d passage For preparation of the antigen 3 or 4 day old W Swiss mice were injected intracerebrally with 0 02 ml of a 10^{-1} dilution obtained from passages 21 24 and 25 28 Mice which were paralyzed two to five days after injection were killed and the brain and cord removed When 15 20 Gm was obtained antigen was prepared by repeated extractions with acetone and ether After the last ether extraction the dry material was resuspended in physiologic saline solution in proportion of 1 part diluent to 1 part central nervous system tissue Supernatant obtained after centrifugation at 10 600 rpm for one hour constituted the antigen Merthiolate® in final dilution of

(4) P oc. Soc E p B l & Med 75 315 318 N mbe 1950

1 10 000 was added and the antigen stored at —20 C The yield of antigen was about 0 66 ml /Gm tissue

With this antigen, the complement fixation test gave specific reactions with immune mouse serum cotton rat immune serum or monkey serum prepared from animals infected with MEF1 strain Complement fixation was not obtained with immune serums prepared against Japanese B and Western equine encephalitis viruses The test could be repeated two or three times with different sets of materials prepared in the same manner

[A practical complement fixation test for poliomyelitis would be a very useful tool for diagnosis and for epidemiologic studies —Ed.]

Milk Borne Poliomyelitis Episode is reported by Michael Lipari[5] (New York State Dept of Health) An unusually high incidence of poliomyelitis in a small area in the northeast section of Delaware County occurred in October 1949 In November the district milk sanitarian reported that dairy C was unsatisfactory because there were no toilet facilities in the plant no soap or paper towels at the handwashing sink milk and cream bottles were not being properly sterilized and the cream was bottled by hand In addition the sanitarian reported that the sole operator in the plant was the father of a child who had recently had poliomyelitis The milk route of dairy C extended through the same area in which the cases of poliomyelitis were occurring

Further study yielded some epidemiologic support to the suspicion that consumption of dairy C milk was the cause of some paralytic and nonparalytic cases in this epidemic There was evidence that the cases due to contact spread complemented the milk borne cases Among a total of 23 paralytic patients 11 from whom a history of contact was elicited showed a consumption rate of dairy C milk of 36 per cent whereas 12 from whom a history of contact was not obtained showed a consumption rate of 92 per cent Among 17 nonparalytic patients 10 from whom a history of contact was elicited showed a consumption rate of dairy C milk of 30 per cent whereas 7 from whom a history of contact was not obtained showed a consumption rate of 86 per cent

Seasonal Distribution of Poliomyelitis Charles Armstrong[6] (Nat l Inst of Health Bethesda Md) states that any

(5) New Y k J Med. 51 362 369 Feb 1 1951
(6) Am. J P b H alth 40 1 96-1304 O tobe 1950

discussion of the seasonal incidence of a disease must take into consideration the method of transmission Whereas occasionally poliomyelitis may be acquired through arthropods food and water evidence is overwhelming that contact is the common means of transmission especially such close contacts as occur in a home Why then is poliomyelitis a disease transmitted by close contact most prevalent when people spend a great amount of time outdoors and why should it tend to wane rapidly during cool weather when they congregate indoors?

One possible explanation is that certain filth associated arthropods which are more prevalent in summer transmit the disease Another theory attributes the summer incidence to an assumed lowering of resistance due to failure of the human defense mechanism to adjust to sudden change from a cool to a warm season especially when temperature variation tends to be great Armstrong prefers the theory that the usual portal of effective entrance for the virus in man may tend to be more permeable during warm than during cold weather This theory does not require assumption of any extra human source of multiplication for the virus any seasonal alteration in the basic resistance of the population or any seasonal variation in virus infectivity It relates the observed seasonal variation to an external mechanism more directly in contact with variable seasonal factors of the environment

Variations in amount and composition of nasopharyngeal secretions may possibly influence seasonal occurrence of poliomyelitis Certainly the disease reaches its highest incidence in temperate climates when upper respiratory infections are at their lowest ebb and secretions from the membranes are tending toward a minimum Whether nasopharyngeal secretions have any specific action or not presence of an abundant secretion on a surface would tend to dilute and to carry away any accompanying virus So far as atmospheric variations may directly affect the respiratory membranes it is important to consider the effect of warming the atmospheric air to the temperature of air within the respiratory passages Expired air is always at about 90 F and 90 per cent saturated with moisture It is therefore the difference between absolute humidity of inspired air and absolute humidity of 90 per cent

saturated air at about 90 F which measures drying effects on the mucous membranes A striking correlation between absolute humidity and incidence of poliomyelitis is clearly apparent Figure 7 shows the average relative humidity of the atmosphere and of the same air when warmed as through inspiration to an assumed temperature of 88 F It also records the reported cases of poliomyelitis for Washington

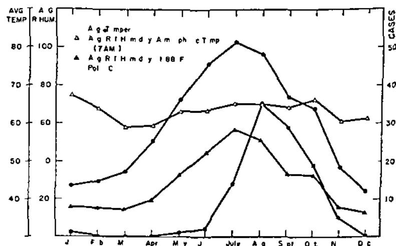


Fig 7 (Courtesy of A m t o g C Am. J P b H lth 40 1 96 1304 October 1950)

D C by month of onset for 1949 The similarity of the last two curves is striking

If seasonal incidence of poliomyelitis is related to the conditions of the portal of entry or of exit for the virus it is conceivable that such conditions might be susceptible to alterations through artificial measures which would tend to hinder effective exposure This concept at least suggests numerous lines for epidemiologic and laboratory investigation

Poliomyelitis and Its Relation to Recent Tonsillectomy J B Dowe[7] (Sydney) points out that among intimate contacts of a poliomyelitis patient the virus is frequently found in nasopharyngeal washings for three days and in stools for up to two months Many attempts have been made to determine why clinical poliomyelitis develops in some but not all persons harboring the virus There may be a delicate bal

(7) M J A tr l a 2 241 243 A g 12 1950

ance between the host s resistance and the virus with precipitation of the disease by any factor lowering the host s resistance such as exposure to extremes of temperature undue fatigue previous or concomitant upper respiratory intestinal or specific infection and nonsurgical or surgical trauma including tonsillectomy

Experimental evidence indicates that if the virus is present in the pharynx at the time of or shortly after pharyngeal operation clinical poliomyelitis may be precipitated and the disease is likely to be of the bulbar type Injection of virus suspension around the tonsil in 20 monkeys was followed by development of poliomyelitis in 18 (13 cases of the bulbar type) Monkeys can be infected by soaking the cut end of the sciatic nerve in a virus suspension Twelve cases of paralytic poliomyelitis were reported after attempts to immunize children with different virus suspensions within 6-14 days of intradermal or subcutaneous injection In all cases paralysis developed first in the inoculated extremity or contralateral one

Statistical evidence also indicates that tonsillectomy in the presence of virus in the pharynx is likely to precipitate clinical poliomyelitis usually in the bulbar form In the 1943 epidemic in Utah poliomyelitis appeared in subjects who had undergone tonsillectomy recently 2 6 times more often than in the general child population and the bulbar form 16 times more often Data from various sources up to 1941 showed that of 87 poliomyelitis cases after recent tonsillectomy 58 were bulbar Almost all developed 7 21 days after tonsillectomy Of 170 patients with poliomyelitis following recent tonsillectomy the bulbar type appeared in 121 (71 per cent) during the first 30 days and in only 20 per cent in the 30-60 day period

In tonsillectomy the efferent motor nerves to the pharyngeal muscles are exposed and the virus may ascend these axons directly to the motor cells of the nucleus ambiguus where it multiplies and produces paralysis In monkeys the virus seems to enter via the protoplasm of the axons of the afferent nerves and the sympathetic nerves of the alimentary and respiratory tracts It multiplies not in the nerves but in the cells of the cranial and spinal ganglions associated with those nerves

Until there is some quick and practical method of determining the presence of poliomyelitis virus in patients in whom

tonsillectomy is contemplated epidemiologic data contraindicate such operations if poliomyelitis is reported in the community or there is possibility of exposure from outside

Poliomyelitis and Immunization against Whooping Cough and Diphtheria H Stanley Banks and A J Beale[8] (London) reviewed records of cases of poliomyelitis in one hospital during 1947 49 for evidence of any relation between onset of poliomyelitis and recent immunization Fourteen (12 6 per cent) such cases were found all in children under 5 among 111 paralytic poliomyelitis patients of all ages There was a preponderance of lower limb paralysis in the group not immunized or immunized over six months before onset of poliomyelitis and a preponderance in contrast of upper limb paralysis in the group immunized within two months of onset of poliomyelitis The latter group with one exception consisted of cases in which the same double event occurred i e (1) inoculation for whooping cough diphtheria or both combined and (2) within two months of one of the injections onset of poliomyelitis with paralysis of a practically uniform pattern in the limb in which inoculation was made In the upper limb muscles of the shoulder girdle and biceps and triceps were invariably the first to be paralyzed and were often the only muscles seriously paralyzed although weakness was not uncommon also in neighboring muscles Occasionally the other arm was also but less extensively affected In the lower limb the pattern was similar muscles of the inoculated buttock and thigh being the earliest and most seriously affected The preponderance of upper limb paralysis in those immunized within two months suggests the influence of the inoculation in determining the site of paralysis since inoculations in London are done much more often in the arm than in the leg

It is concluded that during periods of high or moderately high prevalence of poliomyelitis there is a definite though probably small risk that inoculation for whooping cough and diphtheria prophylaxis will be followed by serious flaccid paralysis of the inoculated limb in young children

[Paralytic accidents following serum injections as well as vaccines are well known (1950 YEAR BOOK OF MEDICINE, p 139 ff) Aside from suggestive seasonal occurrence there is little evidence that they are due to poliomyelitis —Ed.]

(8) Brit M J 2 251 252 July 29 1950

VIRAL HEPATITIS

Studies on Agent of Infectious Hepatitis—*Propagation of Agent in Tissue Culture and in Embryonated Hen's Egg*—Investigations of infectious hepatitis have left little doubt that it is caused by a virus. The agent capable of inducing infectious hepatitis in human volunteers has been found in the duodenal contents, blood and stools of patients during the acute stage of the disease. Since 1945 Werner Henle, Susanna Harris, Gertrude Henle, T. N. Harris, Miles E. Drake, Francoise Mangold and Joseph Stokes, Jr.[9] (Univ. of Pennsylvania) have been attempting to propagate infectious hepatitis virus *in chick embryo or rabbit liver tissue culture. They now* report the procurement of two viral agents from patients with infectious hepatitis in two widely separated outbreaks of the disease. This was done by transfer of acute stage serum and stool filtrates to and passage in tissue cultures of rabbit liver cells *in roller tubes and minced chick embryos in Simms* Sanders medium, followed by passage in the amniotic cavity of the chick. Cultures of both agents, designated the Akiba and NL strains, induced mild hepatitis without jaundice in most volunteers after an incubation period of 9-38 days. Al*though the agents were not identified definitely as the virus* of infectious hepatitis, the evidence supported this conclusion. Final identification, however, must await the development of specific serologic tests.

Disease Produced in Human Volunteers by Agent Cultivated in Tissue Culture or Embryonated Hen's Eggs.—Miles E. Drake, Albert W. Kitts, Mercer C. Blanchard, John D. Farquhar, Joseph Stokes, Jr., and Werner Henle[1] (Univ. of Pennsylvania) report that the virus propagated in tissue culture and in embryonated hen's egg is capable of inducing hep*atitis without jaundice and that the clinical picture is indis*tinguishable from nonicteric hepatitis following infection with natural infectious hepatitis virus. Exposure to natural or cultivated infectious hepatitis virus produced illnesses in comparable percentages of volunteers (83 and 75 per cent *respectively) after similar average incubation periods (24.4*

(9) J. Exp. Med. 92: 271-81, Sept. 1, 1950
(1) Ibid. pp. 283-297

tonsillectomy is contemplated, epidemiologic data contraindicate such operations if poliomyelitis is reported in the community or there is possibility of exposure from outside

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(8) Brit M J 2 251 252 July 29 1950

influenza during the epidemics of 1947 and 1950 None showed rises in titer to the JJ virus although the majority showed typical rises to strains of virus of the A A influenza group However most of them showed moderately high HI titers to the JJ virus thus suggesting that the students had previously had experience with a virus of this type

Since adults because of the high titers might not show a measurable response to infection with this virus attention was directed to young children who would have less experience and whose antibody responses would be more likely to reflect occurrence of infection Serum samples taken from a group of children over a period of months were available These samples showed clear evidence of the prevalence of A influenza When the same serums were tested for HI antibodies against the JJ virus a large number taken in April and May showed a pronounced rise in antibodies as compared with serums taken in the preceding November This indicates a wide exposure to this virus between November and May

The HI reactions obtained with different serum specimens of individual subjects obtained over relatively long periods showed that rises in antibody against both the A strains of influenza virus and the JJ virus occurred when influenza was epidemic

The peculiarities of the hemagglutinating property and growth characteristics of the JJ virus suggested its similarity to the 1233 strain isolated by Taylor in 1947 also during an influenza A epidemic Cross reactions with that virus and with serum obtained from Taylor demonstrated that the JJ and the 1233 strains are essentially identical The fact that both strains were isolated during epidemics of A influenza suggested that the new virus was related to that group of influenza virus The clinical histories and examinations of patients with one or the other illness gave no clearly discriminating differences There was no evidence of the prevalence of any other well recognized disease at the time of the study When pairs of acute and convalescent serums from patients with many other known virus diseases were tested no evidence was found that the JJ virus is related to any of the common virus diseases

Present data indicate that the JJ virus is causally related to a widespread respiratory disease that occurs in epidemic form The frequency with which it causes clinical disease is

and 23 4 days respectively) and of similar average duration (28 3 and 27 6 days respectively) The disease could be divided in both groups of patients into a primary and secondary stage a short interval of relative well being intervening The illnesses in both groups were characterized by anorexia nausea vomiting enlarged tender liver abnormal response to liver function tests and often fever They differed in that jaundice was observed in 31 per cent of the patients infected with natural virus but not in any patient infected with the cultivated virus The absence of jaundice in the latter group suggested that propagation of the infectious hepatitis virus in chick embryo tissues may have led to attenuation of the agent

[Study of this group of viruses has been hampered by the fact that man seemed the only susceptible animal Apparently however the agents can be propagated in the chick embryo This should facilitate work on various aspects of the problem and provide a suitable diagnostic test. In another article (Tr A Am Physicians 63 122 1950) these workers describe a skin test in which chick embryo virus is used as antigen —Ed]

COMMON RESPIRATORY DISEASE

Identification of Another Epidemic Respiratory Disease Thomas Francis Jr J J Quilligan Jr and Elva Minuse (Univ of Michigan) report that during a mild outbreak of influenza associated with A strains of virus in Ann Arbor Mich in spring 1950 several characteristic strains were isolated In addition a virus unrelated to known strains of the influenza group was isolated from fresh throat garglings by amniotic inoculation of chick embryos The person from whom this virus was obtained had an illness similar clinically to a mild form of the influenza prevalent at the time It was characterized by headache and malaise for one day with myalgia at short intervals but no fever Acute and convalescent blood specimens from the patient showed significant rises in hemagglutination inhibiting (HI) titer complement fixing titer and neutralizing titer in eggs Similar tests against A A and B strains of influenza virus showed no rises

To determine the relation of this virus (JJ) to the A epidemic tests were made on 52 pairs of serums obtained from university students in the acute and convalescent stages of

(2) Science 112 495-497 Oct. 27 1950

mental colds was noted between those who received antihistaminic treatment and those who did not Since results were clearcut there seemed no good reason for repeating the experiment with other similar drugs

The second tests were large scale trials of the much weaker antihistamine thonzylamine (also known as neohetramine* or anahist) in colds occurring naturally among the general adult population A total of 1 550 volunteers at 19 different centers were treated 775 with the drug and 775 with control tablets This antihistamine proved of little if any value

Antihistaminic Drugs for Colds Evaluation Based on Controlled Study R J Hoagland E N Deitz P W Myers and H C Cosand (West Point N Y) point out that any treatment for common cold is influenced by so many factors that only a rigidly controlled study eliminating as many variables as possible will provide results on which relatively valid conclusions can be based Some of the variables are suggestibility of the patient and physician fluctuation of immunity difficulty of objective diagnosis unreliability of subjective impressions of a developing head cold until clearcut symptoms such as sniffles occur variable course of a head cold difficulty of follow up and variations in age and general health of patients

The aim of this study made on healthy young men in military service was to eliminate as many variables as possible Medical attention was given before the subject s duties began thus eliminating the temptation of needlessly seeking medical attention to avoid onerous duties Personal prejudice was lessened because physicians prescribing treatment and making follow up examinations were unaware of what medicines the patients were given Five types were used dispensed consecutively by the pharmacists pyribenzamine* hydrochloride in 50 mg tablets tagathen* in 25 mg tablets a placebo resembling pyribenzamine * pyribenzamine* hydrochloride 0 5 per cent solution in a plastic nebulizer and a placebo in a similar nebulizer Oral medicaments were given in a dose of 50 mg five times daily for three days Nebulizer were also used for three days

Cures within 24 hours were reported by 16 per cent of 8 patients with head colds given antihistamines orally 27 pe

(8) J A M A 142 557 160 M y 13 1950

difficult to estimate but in the 1950 epidemic not only children but a significant number of adults were affected

The authors suggest that this virus be called influenza C

Control of Acute Respiratory Illness by Ultraviolet Lights Recently the Westchester County N Y Department of Health studied the channels of flow of measles and chicken pox through a suburban community and investigated the possibilities of interrupting these channels by ultraviolet irradiation of the atmospheres shared by the children of one community Pleasantville Another community Mount Kisco served as a control Despite the complexity of the problem Jean Downes[3] felt it was also worth while to study the morbidity from colds and other acute respiratory illnesses in the two communities

During the first three months of 1946 ultraviolet lights were placed in all the schools of Pleasantville in three of the Sunday schools in the children s room of the library in the village movie and in the Department of Health Clinic rooms Later in the year three churches the Girl and Boy Scout huts and the most patronized soda fountain were equipped

From the data on acute respiratory illness observed in families during three school years in Pleasantville and Mount Kisco it was apparent that introduction of ultraviolet lights in the Pleasantville schools and other places where children congregate did not affect the illness rates Also there was no evidence that the seasonal or weekly incidence of such illness among school age children was affected in any way The two communities were strikingly similar in this respect

[This is important negative evidence since there have been several glowing accounts of significant reduction in re piratory disease rates following ultraviolet light air treatment —Ed]

Clinical Trials of Antihistaminic Drugs in Prevention and Treatment of the Common Cold Report by a Special Committee of the Medical Research Council[4] reviews trials of two kinds The first were small scale tests of two powerful antihistaminic drugs promethazine hydrochloride (phenergan) and chlorocyclizine hydrochloride (histantin) in prevention of experimentally induced colds Neither drug had any effect even when given for two to three days before infection No difference in the nature and duration of experi

(3) Am J P b Health 40 1512 1520 December 1950
(4) B it M J 2 425 429 A g 19 1950

mental colds was noted between those who received antihistaminic treatment and those who did not Since results were clearcut there seemed no good reason for repeating the experiment with other similar drugs

The second tests were large scale trials of the much weaker antihistamine thonzylamine (also known as neohetramine* or anahist) in colds occurring naturally among the general adult population A total of 1 550 volunteers at 19 different centers were treated 775 with the drug and 775 with control tablets This antihistamine proved of little if any value

Antihistaminic Drugs for Colds Evaluation Based on Controlled Study R J Hoagland E N Deitz P W Myers and H C Cosand[5] (West Point N Y) point out that any treatment for common cold is influenced by so many factors that only a rigidly controlled study eliminating as many variables as possible will provide results on which relatively valid conclusions can be based Some of the variables are suggestibility of the patient and physician fluctuation of immunity difficulty of objective diagnosis unreliability of subjective impressions of a developing head cold until clearcut symptoms such as sniffles occur variable course of a head cold difficulty of follow up and variations in age and general health of patients

The aim of this study made on healthy young men in military service was to eliminate as many variables as possible Medical attention was given before the subject s duties began thus eliminating the temptation of needlessly seeking medical attention to avoid onerous duties Personal prejudice was lessened because physicians prescribing treatment and making follow up examinations were unaware of what medicines the patients were given Five types were used dispensed consecutively by the pharmacists pyribenzamine* hydrochloride in 50 mg tablets tagathen* in 25 mg tablets a placebo resembling pyribenzamine * pyribenzamine* hydrochloride 0 5 per cent solution in a plastic nebulizer and a placebo in a similar nebulizer Oral medicaments were given in a dose of 50 mg five times daily for three days Nebulizers were also used for three days

Cures within 24 hours were reported by 16 per cent of 83 patients with head colds given antihistamines orally 27 per

(5) J A M A 143 157 160 May 13 1950

cent of 70 receiving placebos (orally and intranasally) also reported cures Lessened serous nasal discharge was much more common in subjects given antihistamines than in those given placebos Patients receiving pyribenzamine® solution by nebulizer had essentially the same results as those receiving placebos orally and intranasally Essentially the same proportion of patients reported no benefit from orally administered placebos or antihistamines Patients given antihistamines within 24 hours after symptoms began were as likely to fall into the no effect group as into the cured group

***Failure of Antihistaminic Drugs to Prevent or Cure the* Common Cold and Undifferentiated Respiratory Diseases** For two years A E Feller George F Badger Richard G Hodges William S Jordan Jr Charles H Rammelkamp Jr and John H Dingle[6] (Western Reserve Univ) continuously observed the occurrence of illnesses in 55 families During December 1949 and January 1950 voluntary use of antihistamines by members of some of these families allowed assessment of their therapeutic value in well defined circumstances For each family member daily records of presence or absence of symptoms were made usually by the mother Families were asked to report onset of any illness no matter how minor and in most instances one of three physicians visited the home Diagnosis of each respiratory illness was made by the physician observing the patient and was based on the combined data of the family s records the physician s observations the field worker s reports and results of pharyngeal cultures and special examinations In almost all cases the drugs were purchased over the counter and taken in single doses of 25 mg or equivalent amounts

During the two months *376* respiratory illnesses occurred in *203* of the *253* members of the *55* families *87* were treated with antihistamines and 289 were not Three fourths of both treated and control illnesses were common colds Comparison of duration of all illnesses showed that the antihistamines had no beneficial effect regardless of whether dosage was adequate or inadequate Nor was benefit seen in the common cold or other undifferentiated respiratory illnesses Duration of nasal symptoms was *not abbreviated by the antihistamines* Moreover no beneficial effect of the drugs could be shown

(6) New Engl d J M d 42 737 744 M y 11 1950

when adequate dosage was defined as eight or more instead of three or more doses It is concluded that the antihistamines were ineffective for the common cold and other undifferentiated respiratory illnesses

A second study was designed to evaluate prophylactic and therapeutic effect of pyrrolazote* and neohetramine* on occurrence and course of common colds developing after experimental inoculation of normal volunteers Doses of 50 mg four times daily failed to prevent development of colds despite the fact that medication was started before inoculation and continued for several days thereafter

[At least a dozen reports appeared during 1950 concluding that carefully controlled observations failed to substantiate claims for the therapeutic efficacy of antihistaminic drugs against common respiratory disease. It seems a pity that intensive radio and newspaper advertising together with a couple of articles in the *Reader's Digest* can sell us and the lay public such a bill of goods —Ed]

Aureomycin in Treatment of the Common Cold was studied by R J Hoagland E N Deitz P W Myers and H C Cosand[7] (West Point N Y) Because of the effectiveness of *aureomycin in primary atypical pneumonia of unknown etiology* and on many bacterial and nonbacterial micro organisms investigation of its effect on the common cold appeared desirable Any form of treatment for the common cold is influenced by so many factors that only a rigidly controlled study eliminating as many variables as possible will provide results on which relatively valid conclusions can be based An attempt was made in the present investigation to eliminate as many variables as possible

Study of 309 patients with head colds disclosed that cures within 24 hours were reported by 10 4 per cent of 154 patients given aureomycin orally but 9 7 per cent of 155 patients receiving placebos also reported cures Patients receiving 1 Gm [illegible] aureomycin daily and those receiving 2 Gm daily [illegible] the same proportion of cures Practically identical proportions of aureomycin treated and placebo-treated patients [illegible] cures in 24 hours The need for carefully controlled clinical investigation of common cold therapy is further demonstrated since about half the patients receiving inert material reported either moderate improvement or a cure within 24 hours Furthermore essentially the same proportion of patients treated with aureomycin or placebo reported slight or no benefit

(7) N w E gl J M d 243 773 775 N [illegible] 16 1950

ORNITHOSIS

Barnyard Fowl as Source of Human Ornithosis It is known that chickens can carry a psittacosis like virus but few cases of infection with this virus have been reported H Karrer B Eddie and R Schmid[8] (Univ of California) report a case which can be considered an example of clinical ornithosis acquired from chickens

Man 49 chicken farmer had complained of fatigue and general malaise for two months Chills fever (101 103 F) and severe cervico occipital aching had been present for 12 days He had no chest pain dyspnea or sore throat but did have a slightly productive cough with a little yellowish green sputum He had lost 30 lb but did not appear to be particularly ill Aside from fine rales over the base of the right lung and slight decrease in breath sounds results of physical examination were not significant A chest x ray revealed a fine homogeneous infiltration of the right lung The complement fixation reaction with psittacosis antigen was positive in dilutions up to 1 64 The illness followed a benign course and he was discharged after a week

There seemed little doubt as to the infective source So far as could be determined the patient had had no contact with any birds except chickens Positive evidence of ornithotic infection was found among 10 of 20 tested chickens

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MUMPS

Aureomycin in Epidemic Parotitis Wilfred D Langley and John Bryfogle[9] (Sayre Pa) gave three adults with epidemic parotitis 0 5 Gm aureomycin every six hours for eight doses There was dramatic subjective and objective improvement 24 hours after start of treatment Case 1 follows

Girl 19 had had what she thought was a common cold for four days The night before hospitalization she awoke with a painful swelling under the ramus of the right mandible chills and temperature of 103 F The next day the right submaxillary and parotid glands were greatly swollen and tender Left parotid and submaxillary glands were slightly swollen Aureomycin therapy was begun on the following day when glandular involvement had increased

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(8) Cal forn a Med 73 55 57 J ly 1950
(9) J A M A 143 1333 1334 A g 12 1950

Dosage was 500 mg every six hours The next day temperature had fallen and subjective symptoms had cleared appreciably The swelling regressed dramatically in 24 hours Within 48 hours all swelling was gone Convalescence was uneventful

[I am skeptical Others have not had such good luck with antibiotics in therapy of mumps —Ed.]

CHICKENPOX

Varicella Pneumonitis Report of Case with Autopsy Observations is presented by Lester Frank[1] (Univ of Vermont) Chickenpox is rarely fatal and only six autopsy reports have been found in the literature

Woman 34 whose two children had chickenpox first had a generalized papular eruption with appearance of pustules and vesicles two days later On the fourth day she had a frequent cough with production of copious tenacious blood tinged sputum Although she had been fairly well up to this time she became dyspneic and had temperature of 102 F Penicillin therapy was started The next morning temperature pulse rate and blood pressure were normal but the facial lesions had become hemorrhagic That afternoon dyspnea increased and cyanosis appeared She was hospitalized and death occurred shortly afterward on the sixth day of illness

All ections of the lungs showed widespread inflammatory changes Multiple fairly large foci of fibrinous exudation filled the alveoli (Fig 8) elsewhere the same process was diffuse In many areas the fibrin was condensed along alveolar walls to form hyaline lining membranes The cellular exudate was chiefly mononuclear Macrophages were present in large numbers Septal cells were swollen and hyperplastic and often appeared as a continuous layer of cells lining the alveoli Numerous areas of necrosis were distributed throughout the lung Alveolar cells were necrotic The arteries in these areas were also involved in the necrotic process The bronchioles howed severe desquamation of the lining epithelium Gram stains revealed no bacteria. Many large rounded well defined pink intranuclear inclusion bodies were seen within the desquamated septal cells and in an occasional nondesquamated septal cell and bronchiolar epithelial cell (Figs 9 and 10)

Of the other organs only the spleen and esophagus showed significant changes There were numerous shallow ulcers of the esophageal mucosa with chronic inflammation of the submucosa The malpighian corpuscles of the spleen exhibited small foci of necrosis which were also seen to a slight extent in the pulp

Changes found in the lung in varicella pneumonitis are those usually found in other types of virus pneumonia with

(1) A b P th 50 450 456 O tobe 1950



F g 8 (t p) —F b o s x d t on hy l m mb es n o s and large mo o-n cl ph gocyt Hem to yl n phlox n × 100
F g 9 (bott m l ft) —Int lea ncl n bod s tw t al l sept l c ll Hem t yl n phl x e × 900
F g 10 (bottom ght) —Intran l n l n body n b o h ol r p th l al cell Hemat yl n o × 900
(Co t y f F nk L A h P th 50 450 456 O tob 1950)

the addition of characteristic intranuclear inclusion bodies in the septal cells and bronchiolar epithelial cells The general picture is that of patchy bronchopneumonia with areas of con solidation and a tendency toward confluency without suppura tion Except for the characteristic intranuclear inclusions none of the changes are peculiar to varicella pneumonia They have all been found in various combinations in other types of virus pneumonia influenzal pneumonia acute rheumatic fever and radiation pneumonitis

Orchitis in Course of Severe Chickenpox with Pneumo nitis, Followed by Testicular Atrophy, is reported by Conrad Wesselhoeft and C M Pearson[2] (Massachusetts Memorial Hosp Boston) Although chickenpox usually has a simple and uneventful course it can produce formidable manifestations not only in the skin but elsewhere giving rise to a miliary type of pneumonia several forms of encephalitis and nephritis

Man 46 had extensive and typical chickenpox eruption and extreme respiratory distress with cyanosis which began four days after onset of the eruption Chest x rays revealed a characteristic extensive viral type of miliary pneumonia throughout both lung fields Respiratory symptoms improved slowly Five days after hos pitalization he complained of pain in the right testis which was swollen and tender with enlargement of the epididymis This was classified as mild or moderate orchitis the testis did not become hard was only a little more than double its original size and at no time was seriously painful After a week the testis and epididymis returned to normal He was discharged 15 days after ho pitalization Six months later results of physical examination were negative ex cept for the right testis which was a third smaller more irregular softer and somewhat less sensitive than the normal left testis The right epididymis was normal

Definite testicular atrophy six months after acute orchitis in this case is unique and significant it indicates actual de struction of the parenchyma of the testis with subsequent con nective tissue replacement Testicular atrophy has been re ported after orchitis in smallpox but this is the first observa tion of atrophy after orchitis in chickenpox Pneumonitis was probably caused by the varicella virus since the x ray ap pearance was characteristic of viral pneumonia and adequate doses of penicillin and streptomycin were ineffective The negative blood cultures favor viral etiology Furthermore pneumonitis in severe chickenpox in the adult is well known

(2) N w E gl d J M d 24 651 652 Ap 27 1950

SMALLPOX

Studies on Serologic Diagnosis of Smallpox are reported by W A Collier and J K Schonfeld[3] (Pasteur Inst Bandung Indonesia) To diagnose smallpox two procedures may be used demonstration of the virus and serologic methods During the severe smallpox epidemic in Indonesia examination for antibodies against the agglutination of blood corpuscles caused by the virus proved most effective After the outbreak of the epidemic it was advised that nursing personnel without antihemagglutinins be kept out of the smallpox wards So far as is known no case of smallpox occurred in a person shown to have antihemagglutinins

Beginning with the outbreak of the epidemic determination of antihemagglutinins for diagnostic purposes has been done The antihemagglutinin titer is found in the dilution which inhibits completely hemagglutination by the double effective virus dose More than 2 000 specimens of serum of smallpox patients have been examined At the beginning of the illness the titers may be still comparatively low As the illness progresses they rise and reach their maximal level after 12 15 days

Clinically it is difficult during an epidemic to distinguish a light case of variola from a serious case of varicella Consequently during a smallpox epidemic the number of cases of varicella greatly increases This may be partly due to more careful observation and partly to incorrect diagnosis Varicella patients have also been vaccinated and their antihemagglutinins engendered by vaccination must be distinguished from those caused by smallpox If a patient has never been vaccinated even a titer of 1 100 points to variola If the last vaccination was done more than three years previously a titer of 1 800 or higher also points to variola If the serum titer of a recently vaccinated person is lower than 1 3 200 the possibility should be considered that the antibodies are produced by vaccination only In this case the serum must be re examined after two or three days If the titer is then constant it is hardly likely that smallpox is present and the anti

(3) M J A tral 2 363 366 S pt 2 1950

hemagglutinins must be attributed to vaccination A high titer may accompany light infections with smallpox whereas a low titer may be found in serious infections

Comparative Effects of Sulfanilamide and Penicillin on Smallpox. Extensive trial of sulfanilamide in treatment of smallpox in 1942 resulted in the conclusion that sulfanilamide attenuated the virulence of virus as evidenced by reduction of toxemia lowering of mortality rate and reduction of incidence of complications caused by secondary organisms The most important fact was the character of the scabs which were papery and superficial during chemotherapy and left behind after their separation superficial scars without pitting or disfiguration Since few workers have thus far given sufficient trial to antibiotics in smallpox S G Vengsarkar and S S Sabnis[4] (Bombay) treated 49 patients with sulfanilamide and 49 with prophylactic and 49 with curative doses of penicillin Administration of the drug was begun in various stages of the disease Dosage of sulfanilamide (0 5 Gm every four hours in adults) was altered according to the patient s age Prophylactic dosage of sodium penicillin was 10 000 units given intramuscularly at three hour intervals curative dosage 30 000 units given every three hours Medication was discontinued when scab formation began

Total mortality during the observation period was 12 1 per cent excluding moribund patients who died within 48 hours of admission It was 9 per cent in the sulfanilamide series 25 per cent in the prophylactic penicillin series and 2 2 per cent in the curative penicillin series Thus mortality rate was definitely lowered by curative dosage of penicillin as compared with the series treated with sulfanilamide and prophylactic dosage of penicillin Crusting and desiccation were noted by the ninth day (average) of illness in the curative penicillin series and by the tenth and twelfth day (average) in the prophylactic penicillin and sulfanilamide series respectively At time of discharge of patients treated with curative penicillin dosage there was no evidence of excess granulation tissue and pitting was minimal Toxemic manifestations such as insomnia delirium stupor vomiting dehydration and peripheral circulatory failure were rarer in the curative penicillin series than in the prophylactic penicillin

(4) I dia J M S 4 185 190 May 1950

and sulfanilamide series Septic complications such as ab scesses and ulcers were totally absent in the curative penicillin series They were present in the prophylactic penicillin and sulfanilamide series in percentage of 6 8 and 18 1 respectively Lung complications absent in the curative penicillin series were found in 11 3 and 25 per cent in the sulfanilamide and prophylactic penicillin series respectively

[The doses of penicillin used are tiny by our present standards never theless the results appear significant How much of the benefit is due to control of secondary bacterial infection in the pustules?—Ed]

Immediate (So called Immune) Reaction to Smallpox Vaccination is widely interpreted as evidence of immunity to the disease This response however is a manifestation of sensitization to virus fractions and immunity and sensitivity do not necessarily go hand in hand The danger inherent in relying on an immediate reaction after vaccination is empha sized by the occurrence of smallpox among soldiers whose vaccination records indicated that they had shown an im mune response as recently as two to three months before onset of the disease In some of these cases an inert vaccine was probably used Recently recognizing the role of sensi tivity in the immediate reaction workers have relied on mor phologic characteristics such as vesiculation as the criteria of immunity *Abram S Benenson*[5] *(M C U S A) therefore* studied the response of persons vaccinated simultaneously with live and heat killed virus to determine whether there is any morphologic difference between responses to potent and inert vaccines

In 77 persons receiving simultaneous vaccination with live and inactive smallpox virus vaccinoid reactions were ob served only as response to live virus however 8 had no re action to the live virus but the inactivated vaccine produced an immediate reaction The converse was true in three sub jects Fifty six persons had an immediate reaction to both vaccines in 29 they were of the same morphologic type There was no essential difference in the type of immediate response which could be correlated with viability of the vaccinia virus

These observations confirm the contention of others that the immediate reaction after smallpox vaccination is a mani festation of allergic sensitivity to the vaccinia virus which can be induced as readily with killed as with living virus and

(5) J A M A 143 1238 1240 A g 5 1950

does not of itself connote the persistence of adequate immunity An immediate reaction even if vesiculated and surrounded by an areola indicates adequate resistance to virulent smallpox only when the vaccine is known to have been potent Interpretation of the reaction must be based on recognition that the early forms of reaction are not an index of activity of the virus used Any reaction regardless of its forms which is regressing by the fourth day merely indicates sensitivity it connotes immunity only if that lot of vaccine is producing a significant number of vaccinoid or vaccinia reactions in other persons at the same time

Ineffectiveness of Aureomycin in Preventing Primary Vaccinia Reaction The effectiveness of aureomycin in controlling infections caused by certain rickettsias and large viruses suggested that this agent might be active against the vaccinia virus Should this be the case the clinical management of eczema vaccinatum and of secondary vaccination would be improved To test the effectiveness of aureomycin against the vaccinia virus Robert H High and Charles B Reimer[6] (Temple Univ) vaccinated 29 previously unvaccinated white foundlings Sixteen were treated concurrently with aureomycin and 13 served as controls All were vaccinated by the multiple pressure technic on the same day with the same preparation of vaccinia virus

Evolution of the primary vaccinia reaction was not affected by the concurrent administration of aureomycin in doses of approximately 50 mg/kg body weight a day for five days There was no significant difference in the average size of the vaccinia lesions on the third day after inoculation Slightly smaller reactions in the treated group on the seventh day were probably insignificant but may reflect a lesser degree of secondary infection with pyogenic bacteria than in the untreated group

Smallpox Vaccination with Prolonged Vaccinia John A Bigler and Eugene L Slotkowski[7] (Children s Memorial Hosp Chicago) report a case in which in addition to a severe primary vaccination take vaccinia continued to appear over four months until death occurred

Girl 5½ one week after smallpox vaccination had rubeola complicated by bronchopneumonia During this period a primary take

(6) J P d t 38 60 6 J y 1951
(7) Ped t 7 24 33 J y 12 1

occurred Fever continued the vaccination site enlarged and there were pain swelling and tenderness of the left arm She was hospitalized five weeks after vaccination

Over the deltoid region there was a necrotic area about 7 × 7 cm Its border was raised and there was a grayish terraced arrangement In the center was a large blackish necrotic dry crust On the edges of the ulcer and surrounding it were 8 10 vesiculopustular umbilicated lesions with a dry gray central crust The shoulder arm



Fg 11—P t t sho tly b fo e d th N te f ly w ll c r m bed mb h cated, cr sted l n b l w r c nth of ght y (Cou t sy f B gl r J A. and Slotkowsk E L P d t s 7 4 33 Ja y 1951)

and hand were swollen about half again normal size Temperature was elevated up to 104 F daily during the entire illness There were steady loss of weight and increasing toxicity

A paronychia developed on the right middle finger on the 16th hospital day and was opened a week later Eleven days later new vesiculopustular umbilicated crusted lesions began to appear on the left shoulder and the back Eight days later similar lesions appeared on the face and right index finger Three months after admission a new lesion appeared on the right wrist All these lesions became necrotic and were active and present at death Many forms of local and general therapy were used in various combinations but

the lesions steadily progressed and the patient s condition deteri orated (Fig 11)

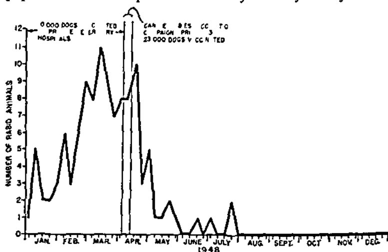
After death sections taken through the border of the necrotic lesion on the left shoulder and right wrist revealed a variety of pathologic changes The greatest changes were found in cells of the malpighian layer These were swollen the cytoplasm had lost its normal character and stained faintly Many of the nuclei had lost their form appeared shriveled and had assumed pe uliar shapes Where the cytoplasm appeared to have undergone liquefaction the vacuoles were separated by strands of tissue which probably repre sented the cell membranes Large multilocular vesicles had formed where cell membrane was destroyed

At the time of autopsy three possibilities were considered as the cause of death (1) The vaccination site acted as a por tal of entry for some infectious agent the part played by vaccination being purely incidental and circumstantial (2) The vaccination site was contaminated by some infectious agent and there was a superimposed change in tissue per meability the Duran Reynals phenomenon (3) The necrotic lesions and death were directly attributable to vaccination the patient having reacted atypically to introduction of the vaccinia virus *for some unknown reason The first possibil* ity was ruled out fairly well by the fact that all aerobic and anaerobic cultures grew bacteria and yeasts which were con sidered contaminants The second possibility could not be ruled out The third possibility was borne out by microscopic examination Sections of skin immediately adjacent to the necrotic areas revealed changes identical to those of the vesiculopustular stage of a primary vaccination take

As a rule the course of a vaccination is quite uniform The lesion passes through the typical stages reaching its full development on the 9th or 10th day followed by drying crusting and scarring Immunologically there is a definite time relationship between introduction of the vaccinia virus and appearance of specific antibodies in the blood These usu ally reach a maximum at the end of the third week Presence of histologically active vaccinial lesions about four months after vaccination could only be explained by the child s in ability to develop immunity to the vaccinia virus Because of this lack of immunity degenerative action of the vaccinia virus continued unopposed

[The authors chose a mild title for the description of a frightful result of vaccinat on —Ed]

Effective Control of Outbreak of Rabies in Memphis and Shelby County, Tenn Ernest S Tierkel (U S Pub Health Service), Lloyd M Graves H G Tuggle and Samuel L Wadley[8] (County Health Dept Memphis) state that the incidence of rabies had been at a substantial endemic level in the dog population of Memphis and Shelby County for years In



F g 12—N mber of rab d n m ls n Memph a d Sb lby C ty by w k befo e and fter t b s camp g (Co rtesy f T e k l E S t l Am J P b Health 40 1084 1088 S ptember 1950)

1944-47 the number of cases reported annually was 42 113 distributed throughout each month of the year However in the early spring of 1948 the incidence began to reach epidemic proportions By the end of March cases were being reported at the rate of more than one/day

An officially sponsored voluntary program was undertaken with canine vaccination as the principal feature Spot maps were prepared to determine the geographic distribution of cases and plans drawn up for a three day program Thirty six emergency dog inoculation clinics were set up in the city and 35 in the county Clinic locations were based on geographic distribution of cases and population concentrations

(8) Am J P b He lth 40 1084 1088 S ptembe 1950

Fire stations schools gasoline service stations country stores and park pavilions were utilized Clinics were open six hours each day Veterinarians supplied and administered the vaccine during the one week emergency program at a charge of $1 00/ dog Public information and education were channeled through every available medium

The public s response and the smoothness and celerity with which the program was executed were impressive The campaign closed with 13 000 dogs vaccinated in the city and 10 000 in the county With the 10 000 vaccinations done rou tinely by practitioners in the three months before the cam paign about 80 per cent of the dog population was immunized

Results of the program were gratifying The number of positive ca es decreased until the last case of animal rabies and the last antirabic vaccine treatment of a human being were reported in July (Fig 12) Both city and county re mained free from rabies for 7½ months These results stand as dramatic testimony to the importance of a well organized vaccination campaign

HODGKIN S DISEASE

Effect of Aureomycin on Hodgkin s Disease Ralph Goldman[9] (Los Angeles) administered standard doses of aureo mycin to five patients in varying stages of Hodgkin s disease all with fever to determine whether an aureomycin suscep tible organism might be an etiologic factor in Hodgkin s dis ease No beneficial effect was apparent Of four patients sub sequently given nitrogen mustard three responded with prompt complete but temporary remission indicating that organisms susceptible to aureomycin play no part in the etiology of Hodgkin s disease

COLLAGEN DISEASES

Rheumatic Fever Treated with Cortisone and ACTH John D Keith and Catherine A Neill[1] (Univ of Toronto) treated 11 boys and 12 girls aged 3 14 with cortisone twice

(9) Am J M S 2 1 195 198 F bru ry 1951
(1) C ad. M A J 64 193 198 M ch 1951

daily (100 200 mg/24 hours) or with ACTH (40 80 mg/24 hours) every 4 hours Treatment usually lasted four to six weeks with retreatment for two to three weeks on evidence of relapse Most patients presented primary attacks of rheumatic fever but four had had previous attacks and two had a history suggesting possible previous attacks

Fever was present in 12 at onset of treatment Temperature returned to normal in an average of 1 8 days in cortisone treated patients and in 24 hours in most of those treated with ACTH Of five patients with arthritis three lost all signs of pain and swelling within 24 hours of start of therapy and two others within 48 hours Subcutaneous nodules disappeared in 19 22 days from the beginning of therapy Of four patients with acute heart failure two responded with dramatic improvement after a few days on ACTH Of four with chronic heart failure three received digoxin and hormone therapy improvement was slow and similar to that usually seen in this condition with the customary therapy but in the fourth hormone was discontinued because of increased failure In some patients the heart became smaller and in others larger during hormone therapy In most sedimentation rate fell to normal in one to three weeks but when the hormone was stopped subsequently or the dose reduced it sometimes rose again and therapy was recommenced Hemoglobin value rose significantly in most patients

Salicylates, Hormones and Penicillin in Treatment of Rheumatic Fever are discussed by Benedict F Massell (House of the Good Samaritan Boston) With the newer hormone preparations still in the experimental stage salicylates remain the drug of choice for rheumatic fever patients not in hospitals equipped for investigative studies Nevertheless preliminary observations indicate that ACTH and cortisone hold considerable promise of being the long sought for remedy in rheumatic fever Penicillin does not appear to have a beneficial effect on the rheumatic process itself but is useful at the time of intercurrent hemolytic streptococcus infections

For many years it was believed that salicylates made rheumatic fever patients more comfortable but did not actually shorten the illness or reduce or prevent heart damage However in 1943 Coburn reported that if massive doses of the

(2) M Cl n No th Ame 34 1419 1434 S pt mbe 1950

drug were given soon after onset of the disease duration of the rheumatic process could be shortened considerably and heart damage prevented Unfortunately most investigators have not been able to equal these good results They have not found massive doses more beneficial than the dosage nec essary for symptomatic relief Even with blood levels above 35 mg./100 cc duration of the rheumatic process has not been shortened or incidence or degree of heart damage re duced Although the sedimentation rate has sometimes been brought to within normal limits by high blood concentrations when the drug was discontinued the rate soon returned to the same level that it would have been without salicylates Fur thermore it appears that the effect of salicylates on the sedi mentation rate is nonspecific and that it may be the result of toxic action on the liver Until the question is definitely answered it seems advisable to give salicylates in sufficient dosage only for symptomatic relief Since by relieving joint pains and abolishing fever salicylates may mask two impor tant manifestations of rheumatic fever and thus produce a false sense of security they should not be given to patients who do not require symptomatic relief or who do not have pericarditis For oral administration either sodium salicylate or aspirin may be used Aspirin is less likely to cause gastric irritation

Occasionally persons are hypersensitive to aspirin Even small doses may be followed by swelling of nasal mucosa puffiness of the eyes and even asthma Epigastric distress nausea and vomiting usually due to direct gastric irritation can be prevented by giving sodium bicarbonate in equal dosage However in patients with severe heart damage there is danger that sodium will cause fluid retention Use of enteric coated preparations is preferable when gastric irritation is a problem in such patients Even with only moderate do age of salicylates some patients will complain of ringing in the ears Salicylates have been shown to cause reduction of plasma pro thrombin However there is generally no need for concern when salicylates are administered in small or moderate doses because actual bleeding as the result of therapy is rare Hyper ventilation is an important sign of serious salicylate intoxi cation and an indication for immediately stopping therapy

From available studies cortisone and ACTH appear to be

potent antirheumatic agents capable of producing effects never before observed with salicylates In Massell s experience with 16 patients with acute rheumatic fever response to ACTH therapy was satisfactory in all but 2 but speed and extent of the response varied Since various dosage schedules were used it was not possible to determine whether clinical variations were due to difference in patients ability to respond or to differences in duration of treatment and variations in individual and total daily dosage Fever and objective arthritis usually subsided in one to three days Subcutaneous nodules became detectably smaller in 7 10 days New nodules did not develop during therapy In some patients sedimentation rates were normal in 6-10 days in others not until after 5 12 weeks of therapy Physical signs of well established and long standing valvular involvement were not affected by ACTH but in three early cases mitral systolic mitral mid diastolic and aortic diastolic murmurs regressed and *ultimately* disappeared in *3 10* weeks *Regression of* cardiac murmurs is not in itself unusual but the findings in the ACTH treated patients were impressive because of the relative rapidity with which the murmurs disappeared and because in two patients the auscultatory signs included a distinct aortic diastolic murmur which has been observed to disappear infrequently Final judgment as to whether ACTH and cortisone can shorten an attack of rheumatic fever must be postponed Nevertheless from the response of these 16 patients the conclusion that in most instances ACTH suppressed the rheumatic process more promptly and completely than previous therapeutic agents seems unavoidable ACTH tends to cause fluid retention and thus to increase previously existing congestive failure or to precipitate the condition in patients with severe rheumatic carditis Massell controlled this complication with a low salt diet and diuretics The only other serious reaction which could be definitely attributed to ACTH was severe mental depression in a woman 21 after treatment for one month Improvement followed omission of ACTH

Experience indicates that streptococcic infections in patients in the active or convalescent stage of rheumatic fever are followed on the average by recrudescences of rheumatic fever in about 50 per cent Before discovery of penicillin there

was not much that could be done to prevent this occurrence Of 34 authentic clinical streptococcic respiratory infections in ambulatory patients 10 were not treated with penicillin and 5 of them were followed by definite recurrences of rheumatic fever The other 24 infections were treated with penicillin in 24-48 hours of onset and not a single one was followed by rheumatic fever For adequate therapy penicillin can be given orally in doses of 200 000 units five times daily Intramuscular injection of procaine penicillin 300 000 units daily may be substituted for oral therapy on one or more days

[Encouraging comments on the value of ACTH and cortisone by an experienced observer Some of our patients have not shown much benefit. There is some evidence that comparatively large doses may be needed for a pronounced effect.—Ed]

Antistreptolysin Titer as Aid in Diagnosis of Rheumatic Fever Antistreptolysin O is an antibody produced in the serum in response to streptococcic infection It neutralizes the O or oxygen labile hemolysin of beta hemolytic streptococci Over three years B B Breese and Hope Gray[3] (Univ of Rochester) had wide experience with this test as a diagnostic aid in rheumatic fever and recommend it for routine use in any state rheumatic fever program

Of 56 patients with active rheumatic fever 95 per cent had antistreptolysin O titers of 250 or over whereas 60 per cent of 39 streptococcic patients 42 per cent of 45 inactive rheumatics and 24 per cent of 160 nonrheumatics had such high titers A repeated low titer is fairly good evidence that a patient does not have active primary rheumatic fever On the other hand a high titer does not mean rheumatic fever is present but merely that the patient has had a beta hemolytic streptococcic infection sometime in the past

[A more elaborate study of this type is described in the next article —Ed.]

Comparative Study of Antihyaluronidase Antistreptolysin 'O' Antistreptokinase and Streptococcus Agglutination Titers in Patients with Rheumatic Fever Acute Hemolytic Streptococcic Infections Rheumatoid Arthritis and Nonrheumatoid Forms of Arthritis Robert W Quinn and Sung J Liao[4] (Yale Univ) noted a rise in titer of streptococcus agglutinins antihyaluronidase antistreptolysin O and antistreptokinase during hemolytic streptococcic infections The

significantly higher mean titers for these antibodies in patients convalescing from streptococcic infections over those for normal subjects illustrates that these tests are sensitive indicators of recent beta hemolytic streptococcic infection The antistreptolysin O and antistreptokinase tests have long been used in this regard and the present results suggest that the antihyaluronidase test is an equally good indicator and has a high degree of specificity

The antienzyme titers (antihyaluronidase antistreptolysin O and antistreptokinase) of patients who acquired rheumatic fever after hemolytic streptococcic infection were significantly higher than those of patients with uncomplicated hemolytic streptococcic infections Furthermore antibody titers remained high longer and returned to lower levels more slowly in patients with rheumatic fever than in those who recovered without complications

Although the number of patients was small and there was some overlapping of the frequency distribution graphs of the four antibodies a general pattern was found for patients with active rheumatic fever rheumatoid and nonrheumatoid arthritis (see the table) In active rheumatic fever titers of

ANTIBODY PATTERNS (TITERS)

Tests	Rheum Fever Active	Rheum Arthritis	Nonrheum Arthritis
Streptococcic antienzyme tests			
1 Antihyaluronidase			
2 Antistreptolysin O	high	low	low
3 Antistreptokinase			
Streptococcic agglutination test with autoclaved bacteria	high	high	low

all four antibodies were high in rheumatoid arthritis only the agglutination titer was high and in nonrheumatoid arthritis no antibody titer was consistently elevated These variations in antibody patterns suggest fundamental differences among these three diseases The agglutination test with autoclaved streptococci cannot be relied on alone as a differential diagnostic test for rheumatic fever and rheumatoid arthritis However on the basis of differences in antibody patterns the agglutination test used in combination with any or all of the antienzyme tests can be recommended for differentiation of

rheumatic fever rheumatoid arthritis and nonrheumatoid arthritis

Arteritis of Striated Muscle in Rheumatoid Arthritis L Sokoloff S L Wilens and J J Bunim[5] (New York Univ) found arteritis in 5 specimens of striated muscle from 57 patients with rheumatoid arthritis Since the tissue was obtained from muscles not situated near joints involved by the arthritic process the vascular lesion cannot be related directly to or



F g 13 (l ft) —A t fl mat mall gm t f t y t l g t d lly I filt t g l k yt t d th gh m d wh h d pt d end th l m s l ft d d t t fi d d l m p te t, H m t yl os d d f m × 192
F g 14 (ght) —Acut fl mm t ry ct t l D ll l nfil t ton t d th o ghout m t f l w ll l m lm t bl t t d H m to yl os ed d f m × 210
(Cou t y f Sok l ff L t l Am J P th 27 157 173 F b y 1951)

considered an extension of these inflammatory changes Furthermore vascular lesions were not observed in 111 specimens of striated muscle from patients with conditions other than rheumatoid arthritis The arteritic lesion must therefore be considered characteristic of rheumatoid arthritis even though its incidence is low 8 8 per cent

Vascular lesions of striated muscle do not appear to have

been described previously in rheumatoid arthritis The lesion is of interest because it adds one more point of similarity to the several that have been recognized between rheumatoid arthritis and rheumatic fever The subcutaneous nodules in both may be strikingly similar histologically Occurrence of arteritis in a small percentage of cases of rheumatic fever though not usually in striated muscle is well recognized The arteritis of rheumatoid arthritis may have much the same basis as that of the rheumatic state It is of interest also that

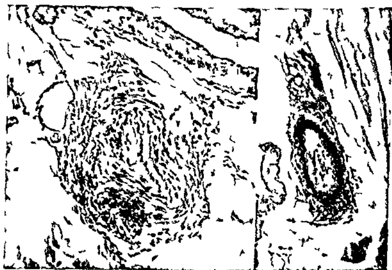


Fig 15 (left) —S b t fl mm to y ct n n d tit f m ll arte y Exudat is und g g gan t o and pl m nt by fib ous t e R act on s l m t d to m g n of ess l H mat xyl n os d c d f om × 210
Fig 16 (right) —Infl mm to y r a t o xt nd g th ough t wall f a teriol Int m s n ent ally tl ke l last a i t t Hemat yl n e s r d ced f om × 10
(Cou t y f k l ff L et l Am J P th 27 157 173 F bruary 1951)

arteritic lesions have been recognized in a number of conditions in which allergic phenomena are prominent and in those in which destruction of collagen is a conspicuous feature of the lesions These include periarteritis nodosa rheumatic fever serum sickness and lupus erythematosus Rheumatoid arthritis has sometimes been included in these groups of diseases

There were no distinctive features that sharply differentiated this form of arteritis from other recognized varieties

but there was an obvious uniformity and consistency in the major features (Figs 13 16) The adventitia regularly showed the most pronounced change and in some instances was the only coat appreciably involved However the inflam matory changes often spread through all three layers the lesion may therefore be termed panarteritis Composition of the cellular exudate was varied but the usual types of cells found in granulomatous lesions were encountered Poly morphonuclear neutrophils predominated in some lesions whereas in others presumably older mononuclear forms were more conspicuous The process was limited to very small arteries Specificity of the arteritis in striated muscle in rheumatoid arthritis depends chiefly on location of the lesion size of the artery involved and association with joint or sub cutaneous lesions rather than on any distinctive quality of the inflammatory process itself Clinical and pathologic data in *the cases studied* were *sufficiently diverse to indicate* that the vascular lesion is not readily associated with any particular feature of rheumatoid arthritis

Periarteritis Occurring during Propylthiouracil Therapy Although periarteritis nodosa due to thiourea has been re ported Robert V McCormick[6] (New York City) reports a case which is the first to show that propylthiouracil may cause fatal generalized periarteritis

Woman had been hypersensitive and irritable for four months after emotional trauma She had a palpable thyroid and a basal metabolic rate of + 53 per cent Blood pressure was 210/100 and *pulse rate 100 the heart was enlarged with a blowing systolic mur* mur at the apex She was given propylthiouracil 50 mg four times daily for 10 days She then reduced the dose herself to half this amount because of gastric irritation and in five days stopped taking the drug

At the next examination fibrillation at a rate of 180 was noted and she was hospitalized *A few rales of congestive failure* were heard at both lung bases There was no evidence of peripheral edema and reflexes were normal Because her age and condition made her a poor operative risk she was again given propylthiouracil 50 mg four times daily Temperature was normal before administration but in the following 24 hours it rose to 103 4 F and diarrhea devel oped About 36 hours after administration she became incontinent and unable to care for herself She had difficulty forming words became irrational showed left facial paresis with weakness and had a Babinski reflex on the left side Spinal tap done because a cerebral

(6) J A M A 144 1453 1454 D 23 1950

vascular accident was suspected revealed no abnormalities At this time the white blood cell count was 7 150 with 90 per cent neutrophils On the fifth day of this episode it was noted that all the symptoms had become apparent in 24 hours after propylthiouracil administration use of the drug was therefore stopped. Within 24 hours temperature was normal diarrhea stopped the Babinski reflex disappeared and she became rational

The patient was followed in the clinic for two months during which time she was asymptomatic She was then inadvertently given propylthiouracil 50 mg four times daily She had taken a total of 1 150 mg when she became unconscious and was brought to the hospital two hours later There was evidence of a left cerebral vascular accident left facial weakness and a left Babinski reflex but spinal tap revealed no abnormalities Supportive therapy was given but her condition remained unchanged and she died six days after admission Autopsy revealed diffuse periarteritis

Role of Sulfonamides and Penicillin in Pathogenesis of Systemic Lupus Erythematosus The statement that systemic lupus erythematosus is on the increase is supported by a welter of reports from the United States Continental Europe and the United Kingdom Although its cause is uncertain fragments of the puzzle are being pieced together and the concept of a suitable soil (endocrine age sex) and essential sensitizers (bacterial drug and protein antigens) with trigger factors (actinic rays) is accepted by most workers

Stephen Gold[7] (St George s Hosp London) reports eight cases because they were all seen in the same six months which supports the view that the condition is no longer rare and each patient had received penicillin or one or more courses of sulfonamides before lupus erythematosus became systemic Five had been treated with sulfonamides before dissemination Penicillin was given therapeutically to four patients in two it had a dramatic effect and seemed to precipitate their death one almost died and one seemed unaffected Five of the eight patients died three were in a subacute phase when last seen

No definite conclusions could be drawn from these cases the figures were in no way significant although suggestive This much was certain the pararheumatic diseases are becoming common and the rise in incidence has followed the introduction of sulfonamides Sulfonamides are not the only causative factor but they are one potent factor It is probably unwise to administer sulfonamides to a patient with chronic

(7) Lancet 1 268 272 Feb 3 1951

discoid lupus erythematosus and extremely dangerous to give them in an acute case The fact that one short course so long as sulfonamides have never been given before may cause no ill effect may be the reason for the early reports of the beneficial effects of sulfonamides in lupus erythematosus

Much the same can be said of penicillin but with less conviction It will be interesting to see if repeated injections of penicillin into rabbits can produce polyarteritis nodosa lesions The more that is seen of these patients the more impressive is the fact that they may be intolerant of many drugs and they seem to do better on no drug than on any available ones Use in a hypersensitivity disease of drugs known to be sensitizers should be abandoned

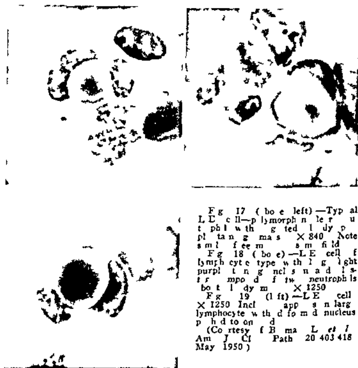
[We certainly seem to be seeing more cases of lupus erythematosus now than 10 or 15 years ago This may be partly attributable to increased intere t, more frequent diagnosi in the abs nce of kin lesions and introduction of the L E cell test (ee next article) —Ed]

So called Lupus Erythematosus Inclusion Phenomenon of Bone Marrow and Blood Morphologic and Serologic Studies *As originally described the L E cell seen in marrow smears of patients with acute disseminated lupus erythematosus* was almost always a mature polymorphonuclear neutrophil which appeared to have phagocytized a homogeneous purple staining mass of chromatin (Fig 17) Lawrence Berman Arnold R Axelrod Herbert L Goodman and Robert I McClaughry[8] (Wayne Univ) observed the common occurrence of the inclusion phenomenon in band form as well as in polymorphonuclear neutrophils and its occasional presence in eosinophils monocytes and lymphocytes (Figs 18 and 19) The inclusions vary greatly in size shape density and staining property The phenomena are in part dependent on the technics used in preparing the marrow material The authors use smears obtained from the first drop of aspirated marrow in addition to smears from suspensions of the buffy layer of centrifuged heparinized material The L E cell has not been observed in direct smears imprints or sections of aspirated marrow but only in centrifuged heparinized citrated or oxalated specimens Further study of the effect of anticoagulants is indicated

When there are few L E cells examination of smears may become tedious and time consuming To obtain material

(8) Am J Cl P th 0 403 418 M y 1950

suitable for rapid diagnostic scanning the authors tried var ious types of *fixation and staining Fixation of wet smears* in absolute methyl alcohol causes shrinkage of the ingested masses so that they are easily discovered under the low power objective If the Papanicolaou stain is used the smears con tain predominantly greenish gray images of the various cells



F g 17 (bo e left) —Typ al L E c ll—p lymorph n le r u t ph l w th g ted l dy p pl ta n g ma s × 840 Note s m l f ee m s m fi ld
F g 18 (bo e) —L E cell f lymph cyt e type w th l g l ght purpl t n g ncl s n a d l s t r mpo d f tw neutroph ls bo t l dy m × 1250
F g 19 (l ft) —L E cell × 1250 Incl app s n larg lymphocyte w th d fo m d nucleus p h d to on d
(Co rtesy f B ma L *et l* Am J Cl Path 20 403 418 May 1950)

The appearance of L E cells is striking because of their pecul iar bull s eye structure This type of preparation can be recommended for rapid scanning For quantitative studies air dried Wright stained material is preferable because with wet fixation some of the cells may be washed off

As yet there are insufficient data for determining the fre quency of the L E phenomena in patients with various types of lupus erythematosus or in persons without the disease From evidence available however it appears that the phe

nomena are likely to be present in smears of centrifuged heparinized citrated or oxalated marrow from patients with acute disseminated lupus erythematosus but are not likely to be found in marrow from patients with other diseases including related conditions falling within the collagen disease group or even with subacute or chronic lupus erythematosus When the cells are found in the marrow of the nonlupus group the number is relatively low The finding of a rare L E cell in marrow smears therefore does not establish a diagnosis of acute lupus erythematosus but for the present a ratio of about 10 or more cells/500 neutrophils has practical diagnostic importance

An important observation of the formation of the L E phenomena in vitro was made by Haserick and Bortz The simple procedure of placing cells from the buffy layer of heparinized marrow from normal persons in contact with cell free plasma from patients with acute disseminated lupus erythematosus (L E plasma) produces all the L E phenomena in smears made from preparations of the concentrate of the mixture The in vitro test constitutes a simple and convenient adjunct to laboratory diagnosis of the disease The authors have not found it necessary to incubate the plasma marrow mixtures as the typical changes are seen after centrifugation for five minutes at room temperature Discovery of an L E plasma factor capable of provoking the L E phenomena in marrow material not previously exhibiting them opens many portals for research on the pathogenesis of lupus erythematosus Of immediate practical importance is development of the in vitro test as a diagnostic procedure Although no adequate control studies have been reported the authors know of approximately 50 in vitro tests with plasma from patients with diseases of the so called collagen disease group leukopenia of unspecified cause and cirrhosis of the liver or hyperglobulinemia all of which gave negative results It seems safe to assume that the test is valuable and practically specific Present data indicate that marrow from patients with a variety of diseases is capable of reacting to contact with L E plasma although in different degrees A single inconclusive in vitro reaction does not entirely rule out activity of the plasma as the poor reaction may be due to the relatively poor reactibility of the test cells

ACTH and Cortisone in Diffuse Collagen Disease and Chronic Dermatoses Differential Therapeutic Effects Edward N Irons John P Ayer R Gordon Brown and S Howard Armstrong Jr[9] (Univ of Illinois) treated eight patients with disseminated lupus erythematosus and eight with miscellaneous diffuse collagen disease six of whom had chronic dermatoses *Initial dosage of ACTH was 100 mg daily in* four to six divided doses for two or three days and of cortisone 200 mg/day in single doses In these cases in contrast with the initial 24 hour response to ACTH 7 days of cortisone therapy passed before temperature subsided In lupus patients serious complications when ACTH therapy was prolonged led to a plan of treatment in which cortisone was used to hold remissions obtained by initial ACTH administration For initiating remissions ACTH the preferred drug should be administered 10 days to 2 weeks for optimal benefit Prolonged therapy with large doses of ACTH or cortisone should not be used in polyarteritis because of the occlusive tendency during healing

Eosinophil counts in these patients showed so many exceptions to the expected drop that eosinophil response could not be used as evidence of clinical improvement due to ACTH For definitive evidence of adrenal response in initiating ACTH therapy eosinophil response alone is not reliable In diffuse collagen disease such as lupus characterized by leukopenia a shift was observed to moderate leukocytosis during ACTH cortisone therapy A return to leukopenia constituted an early sign of exacerbation on decreased amounts of drug Albuminuria hematuria and cylindruria diminished or cleared in all patients studied Abnormal plasma protein levels showed various degrees of reversion to normal Erythrocyte sedimentation rate which was elevated in all patients studied fell in all but reached normal limits in only two

Complications included moderate to pronounced water retention manifested by rapid weight gain and edema in nine patients despite rigorous adherence to the low sodium diet In most instances mercurial diuretics were successful in controlling excessive edema Sodium and potassium outputs or at least chloride output should be checked before during and after diuresis in each patient When symptoms of potassium

(9) J A M A 145 861 869 M 24 1951

insufficiency are noted mercurials should be abandoned and reduction or discontinuance of ACTH or cortisone considered seriously Such symptoms include muscle weakness cardio vascular collapse with associated ECG changes and sometimes striking abdominal distention cramps and pain which sug gest a surgical abdominal emergency Lack of localizing signs of peritoneal irritation and a lowered serum potassium value (1 8 2 5 m Eq /L) should aid differentiation In pre venting this syndrome many days of urinary loss of potas sium precede development of clinical symptoms and drop of serum potassium to abnormal levels Oral intake of up to *6 Gm* potassium chloride or potassium bicarbonate a day has sufficed to avert complications Once developed potassium deficiency is difficult to treat for potassium salts taken orally are not well tolerated and intravenous solutions in excess of 3 per cent concentration cause painful venous spasm

Other complications included tendency to constant cold perspiration in patients on prolonged cortisone therapy and one or more of the features characteristic of Cushing s syn drome The latter changes developed in 10 of 13 patients All patients receiving these drugs had a moderate to pronounced increase in well being Of more serious import were episodes of severe depression hypomania or frank schizoid psychoses in five patients receiving ACTH The drug was discontinued and subsequent cortisone therapy carried out successfully without recurrence of the psychoses The type of psychotic manifestation appears related to the underlying psychologic structure of the patient under treatment

Effect of Cortisone in Glomerulonephritis and Nephrop athy of Disseminated Lupus Erythematosus The dramatic response of certain hypersensitivity diseases to ACTH and cortisone suggested that they might favorably affect the course of glomerulonephritis and the nephropathy of dissemi nated lupus erythematosus B I Heller W E Jacobson and J F Hammarsten[1] (Univ of Minnesota) therefore gave cor tisone to four patients in the various phases of glomerulone phritis and two with the nephropathy of disseminated lupus erythematosus Although transient changes in renal function occurred during cortisone therapy hematuria and albuminuria did not abate and in some cases actually increased Thus cor

(1) J Lab & Cl M d 37 133 142 J n y 1951

tisone had no beneficial effect on the basic pathologic process in the glomerular capillaries

Temporal Arteritis Two Cases Treated with Aureomycin The syndrome of temporal arteritis occurs in elderly patients and is characterized by an inflammatory reaction in the temporal arteries with headache and signs of constitutional disturbance including fever sweats anorexia and weight loss The temporal arteries are thickened and tortuous and the overlying skin is often reddened In some cases the disease spreads to the retinal vessels and disturbs vision White cell count may be normal or show leukocytosis and erythrocyte sedimentation rate is almost constantly increased Etiology remains obscure but in view of the inflammatory changes in the walls of the affected vessels and the fever infection seems the most likely cause No report on response of temporal arteritis to any of the known chemotherapeutic or antibiotic agents has appeared

J M Rice Oxley and A M Cooke (Radcliffe Infirm Oxford) treated two patients with aureomycin in the usual doses In one case biopsy confirmed the diagnosis of temporal arteritis and in the other although biopsy was not done the clinical manifestations were conclusive One patient improved steadily on aureomycin (0 5 Gm every six hours) with remarkable change in appearance and after two weeks was afebrile and symptom free In the second patient the drug was poorly tolerated and its effect less conclusive yet a definite influence was apparent in fall of temperature and return to normal of the temporal arteries soon after start of aureomycin therapy and relapse 48 hours after stoppage Although results of treatment in two cases are not conclusive the response was encouraging enough to warrant trial of aureomycin by other workers

[There is surely no harm in trying aureomycin in this painful and sometimes serious affliction but we need more evidence before concluding that it is effective —Ed]

Generalized Scleredema Report with Autopsy Findings Since 1900 when this syndrome was described 103 cases have been reported Its systemic nature was suggested by Vallee That the skin is not the only system affected was noted by several authors whose patients had hydrarthroses

( ) L t 1 89 90 Jan 13 1951

Irving Leinward[3] (New York City) presents confirmatory autopsy evidence of the systemic nature of the disease

Woman 58 was hospitalized in 1942 with a history of progressive stiffening of the skin for 10 month Cold aggravated the disease and stiffness was accompanied by pain on motion General health had been good and there had been no preceding acute infection and no history of allergy Examination revealed stiffened skin over the face neck shoulders and arms down to the elbow and back and over the abdomen down to the umbilicus The skin of the breasts was soft but the medullary tissue leathery Biopsy revealed skin compatible with that seen in scleredema The only significant laboratory finding was mild anemia

She grew slowly but progressively worse and in 1946 began to have exertional dyspnea In February 1947 she was again hospitalized the chief complaint being difficulty in breathing pain in the back cough and fever for three weeks Moist rales were audible throughout both lungs posteriorly more pronounced at the bases A systolic murmur was heard over the entire precordium rhythm was regular pulse rate was 104 and heart sounds were muffled Palpation of the abdomen was difficult due to thickening of the skin and slight distention of the colon but it was thought that the liver was 3 fingerbreadths below the costal margin The entire body appeared to be sheathed in a plastic rubber replica of the skin The skin was pale yellow and could not be creased in folds Pressure did not produce pitting She did not respond to digitalization Cardiac failure was thought largely due to severe anemia. She became comatose and died nine days after admission

At autopsy diffuse distribution of edema and absence of any other striking pathologic involvement was impressive Gross examination revealed effusions in the pleural pericardial and peritoneal cavities Edema and a peculiar rubbery consistency of many of the viscera sufficient to hold the tissues rigid after section were noted Findings otherwise were not remarkable Microscopic examination of the skin revealed swelling of the collagen with separation of the bundles resulting in clear spaces These could easily be mistaken for artefacts reproduced in cutting sections The absence of any inflammatory reaction only served to further this impression The microscopic picture in the viscera was the same as seen in the skin The edema present was sufficient to interfere with the normal function of the affected tissue

Distribution and progression of the skin lesions in this case were characteristic The tissues of the neck were so adherent to each other that they could scarcely be separated at autopsy Only the hands and feet remained uninvolved The skin changes were typical and the waxy feeling was unmistakable

(3) A I t Med 34 226-38 J y 1951

Scleredema must be differentiated from scleroderma and dermatomyositis which it closely resembles in the acute phase In scleredema the hands and feet are never affected There is no pigmentation or calcinosis in the skin and no atrophy of muscle The skin is not atrophied Raynaud s syndrome is usually absent Pathologically the epidermis is not affected the process being in the deeper portion of the skin and subcutaneous tissue There is no inflammatory reaction or endarteritis In scleroderma the superficial skin layers are often involved and a cellular reaction is usually present about the blood vessels There is sclerosis of the underlying tissue so that the tissue is thick and hard The hands are always involved There is frequently bronze pigmentation of the skin Calcinosis sometimes occurs and atrophy of underlying muscle is common Dermatomyositis may offer some differential problem It is usually progressive and prostrating Erythematous skin lesions may be present and weakness muscle pain atrophy and fever are usually prominent

In cases in the literature in which complaints were noted many symptoms referable to visceral involvement were found Dysphagia was common Swelling of the tongue and pharynx hydrothorax and pericardial effusion have been reported Apparently these were systemic lesions which appeared concurrently with skin lesions and disappeared with involution of the surface lesion

The pathologic changes in scleredema consist chiefly of thickening and hyalinization of the collagen bundles with production or deposition of a mucin like material between the fibers Since these changes occur throughout the body it seems logical to include this disease among the diseases of the collagen system This classification is particularly applicable in view of the fact that the pathogenesis of disease of the collagen system is probably concerned mainly with the intercellular substance

[This entity is not well known and unfortunately the similarity in names may cause confusion with scleroderma The recognition of scleredema as a systemic disease with the possibility of diffuse visceral involvement is important —Ed]

General Pathology of Virus Infections It is difficult to see any common features in the pathology or immunology of virus infections such as measles influenza and herpes simplex Among these and other human virus infections are diseases of short or long incubation some that confer lifelong immunity some that persist like trachoma or recur like herpes simplex and some that show short lasting immunity such as the respiratory infections F M Burnet[4] (Univ of Melbourne) attempts to find common factors within this multiform behavior of human virus diseases

A virus is a parasitic micro organism smaller than most bacteria which is capable of multiplication only with living susceptible host cells To multiply the virus particle must pass through the cell surface into the interior For viruses without marked tissue specificity and especially for those introduced into the body through a traumatized area it is *reasonable to assume that no specific mechanism for passage* through the cell surface is necessary In yellow fever the trauma required is the mosquito bite

Hirst discovered a most effective tool for study of the interaction of influenza virus and the cell surface—the hemagglutination reaction He first showed that agglutination of red cells is associated with adsorption of the virus onto the cell surface There is adequate evidence that agglutination is simply due to the fact that by adsorption of a virus particle to two adjacent cells a bridge between the two can be formed Hirst next showed that if a mixture of virus and red cells is kept at 37 C with intermittent shaking and the proportions of the virus free and bound to the cells respectively are estimated at suitable periods a regular sequence of adsorption and elution is observed The virus is first rapidly and almost completely removed from the fluid after an hour or two it begins to reappear and eventually is present in virtually its original amount Simultaneously the red cells have ceased to be agglutinated If they are collected washed and retested with fresh virus they are quite inagglutinable The

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(4) 059 1063 J 10 1950

eluted virus is still fully capable of producing the same sequence of effects on fresh cells In other words the virus displays all the characteristics of enzymic action The sequence can be described as adsorption of virus particles onto receptors of the cell surface with subsequent destruction of receptors and release of virus These experiments were done with red cells which are not susceptible to infection by influenza virus However all the essential phenomena shown by the red cell surface can be duplicated by use of the cells lining the respiratory tract In the living animal virus introduced into the lung via the trachea is absorbed but not released The virus units instead enter the cells initiating infection The receptor substance which is both the cell component responsible for adsorbing the virus and the substrate of its enzyme is believed to be a mucopolysaccharide probably present in the form of a meshwork on the cell surface and intimately related to lipid and protein components It has been reported recently that another group of viruses responsible for encephalitis in animals will agglutinate mammalian red cells

A virus particle enters a susceptible cell In a few hours the cell has disintegrated and perhaps 50 or 100 fresh virus particles have been set free What happens within the cell between entry of the virus and liberation of the new generation is being studied Histochemical methods have shown that in the early stages of infection with several viruses there is a great increase in the cytoplasmic concentration of ribonucleic acid This is generally interpreted as indicating increased protein synthetic activity in the cell Other studies have shown that if one type of influenza virus which cannot multiply in certain cells enters them first they are incapable of supporting multiplication of another strain which would normally flourish there There are a number of puzzling phenomena which may be related to this interference latent infection being one All these phenomena suggest that there is some delicate balance within the cell which determines whether an entrant virus will flourish

As a working hypothesis applied specifically to the influenza virus it is suggested that the virus particle on entering the susceptible cell breaks into a relatively large number of subunits which are essentially self reproducing entities

Each is small enough to make some necessary intimate contact with a cellular enzyme system which can provide for replication of the virus subunit the necessary flow of energy and building stones As replication proceeds there is a drain on the protein synthetic mechanism of the cell shown first by increase in ribonucleic acid and later as the whole structure begins to break down by gross morphologic changes From the pool of many thousand subunits present toward the end of the process there is a reaggregation into the appropriate bundles that make up the infective virus particle

Studies of mousepox indicated that in any virus disease with a long incubation period the following sequence can be expected a site of primary infection and multiplication passage of the virus to those organs best equipped to remove foreign particles from lymph or blood multiplication in lymphoid tissue spleen or liver with eventual liberation in much greater concentration into the blood symptomatic infection of the skin general mucous membranes or other organs relatively rapid appearance of antibody with recovery unless the initial onslaught was too severe Experiments with influenza virus suggest a different situation Infection in mice was initiated by administering the virus intranasally and virus multiplication was limited to the cells lining the respiratory tract Only the respiratory epithelium was directly involved Infection by viruses of this type is infection over the surface of a sheet of susceptible cells Passage of virus into lymph channels undoubtedly occurs and probably small amounts reach the blood in neither case is the virus conveyed to susceptible cells This surface character of the infection is of great significance in understanding the part played by immunity in influenza

Little work has been done on the means by which symptoms are produced in virus disease Intensity of symptoms is probably best considered as essentially a measure of cell damage the symptom producing agents being soluble products of cell breakdown The more sudden the liberation of such products the more acute the symptoms On the basis of this view sudden onset of symptoms in influenza could be associated with the infection and damage of a large area of bronchiolar epithelium There is nothing to suggest that it is a manifestation of blood stream invasion by the virus

There is one generalization regarding immunity in virus disease which appears to be without exception Antibody is effective in preventing infection of a cell if it can make con tact in adequate concentration with the virus particle before it enters the cell In yellow fever the conditions for fulfilling this requirement are ideal The primary infection is asso ciated with a veritable flooding of the blood and tissues with virus providing an intense stimulus to antibody production When an immune person is bitten by an infected mosquito the virus must be exposed to maximal antibody concentration in the blood before it can reach the liver or any other suitable nidus for its multiplication In influenza the virus spreads from cell to cell in the film of liquid bathing the surface of the respiratory epithelium It is difficult to guess what is the ac tual concentration of antibody in the normal film in terms of that in the blood but it is almost certainly considerably lower

It is probably fair to summarize the opinion of most work ers with virus disease as a belief that in any virus disease in which effective invasion of susceptible tissues occurs recov ery and subsequent immunity are functions of production of circulating antibody The effectiveness of that antibody is determined by the considerations of access to the virus par ticle before it can enter the susceptible cell

[Burnet s writings are particularly stimulating He is not only an outstanding microbiologist but is unusual by virtue of his willingness to speculate on the broad implications of scientific work —Ed]

Relation of Nutritional Deficiency in Man to Antibody Production Investigators working on the relationship of nu tritional and specific vitamin deficiency to antibody response and resistance to infection in animals have obtained conflict ing results Experiments in which the agglutination and hemo lytic reactions were used to measure antibody levels indicated that protein depleted rabbits and rats do not produce as much antibody as nondepleted controls However studies of the effects of prolonged protein starvation on production of ag glutinins in rats and of amboceptor and complement in guinea pigs have shown that despite almost complete restriction of growth in the animals agglutinin and amboceptor titers were as high as those obtained with animals on an adequate diet Restriction of protein intake for 28 weeks did not signifi cantly lower the complement level Similarly rats on a pro tein-deficient diet have been shown to be no less resistant to

infection with virulent Salmonella typhimurium than well nourished controls Furthermore the protein deficient rats attained antibody titers equivalent to those of the well nourished animals in response to infection

Henry H Balch[5] (New York Univ) studied the antibody response in 25 patients depleted nutritionally by disease and in 19 controls The depleted patients were all severely ill with long standing disease and progressive weight loss In contrast with previous investigations quantitative methods were used to measure the amount of antibody formed Diphtheria antitoxin production after a single constant dose of highly purified toxoid given intramuscularly to Schick negative persons was the method used for estimating antibody producing capacity This system was chosen because the antigen is available as a highly purified and well characterized protein the antitoxin response in persons already Schick negative is high and fairly uniform and circulating diphtheria antitoxin can be measured accurately even in low concentrations by the intracutaneous test in the rabbit In most cases titers are sufficiently high so that antitoxin content can be checked by the quantitative precipitin reaction

Results showed that nutritionally depleted patients can produce large quantities of antibody There was little difference in rate of antibody synthesis between depleted and healthy adults This study also confirmed previous observations that antibody production in man is subject to individual variation It could not be related to age initial antibody level or total serum protein albumin or globulin levels No direct relation was found between antibody producing capacity and appearance of infection

This study does not show whether high protein diets influence antibody production It does show however that healthy patients on a high protein diet may not produce as much antibody as dying wasted patients on a minimal diet who are also in negative nitrogen balance It seems likely therefore that high protein diets may be of minor importance in increasing resistance to infection through the mechanism of acquired immunity

Experimental Hypersensitivity in the Rabbit The effect of inhibition of antibody formation by x radiation and nitro

(5) J Imm l 64 397 410 M y 1950

gen mustards on the histologic and serologic sequences and on the behavior of serum complement after single large injections of foreign proteins was studied by Louis Schwab Frederick C Moll Thomas Hall Henry Brean Marjorie Kirk Clinton Van Zandt Hawn and Charles A Janeway[6] Responses of rabbits to single large intravenous injections of purified bovine serum proteins were recently described by Hawn and Janeway In most animals given bovine serum gamma globulin transient intracapillary glomerulonephritis developed with focal lesions of the liver heart and joints the acute phase occurring one to two weeks after injection In about half the rabbits given crystallized bovine serum albumin an intimal and subintimal arteritis of the large pulmonary and systemic arteries developed the acute lesions being seen two to three weeks after injection The antigen gamma globulin regularly disappeared from the circulation in 8 14 days after injection and homologous antibody appeared shortly thereafter In contrast albumin disappeared from the circulation after 14 21 days and then only in some rabbits From this correlation of times of disappearance of the antigens of emergence of their antibodies and of development of lesions it was deduced that the lesions are dependent on a reaction between antigen and antibody Furthermore it was postulated that the difference in distribution of the lesions depended on a difference in localization of the two proteins used as antigens It was further assumed that if the localization of the antigen is the determining factor in distribution of lesions the reaction producing the lesions must involve antigen fixed in or on tissue cells and antibody elaborated locally or transported possibly by cells from other sites of antibody formation The corollary to the conception that these lesions result from the reaction of antibody and fixed antigen is that circulating antigen is of secondary importance to fixed antigen in the pathogenesis of localized tissue damage

The authors therefore attempted to find whether the lesions observed in rabbits after a single large intravenous injection of foreign protein are actually dependent on antibody formation X radiation and injection of nitrogen mustards were used to suppress antibody formation in the experimental animals and their tissue responses after injection of bovine

(6) J Exp Med 91 505 5 6 May 1950

serum gamma globulin were compared with those of control animals

Results showed that x radiation and nitrogen mustards inhibit antibody formation and that when they are used before intravenous injections of bovine serum gamma globulin the tissue lesions ordinarily seen 7 10 days thereafter generally fail to develop These facts support the thesis that these lesions are directly related to antibody development and are *not merely toxic reactions to foreign protein It was also dem*onstrated that there are close correlations in time between depression of serum complement and disappearance of antigen from the circulation on the one hand and return of serum complement to normal levels and appearance of homologous antibody on the other and further that there is a correlation between these events and development of tissue lesions The sudden fall in complement titer does not occur when antibody formation is inhibited

Localization of Antigen in Tissue Cells Fate of Injected Foreign Proteins in Mouse Earlier articles in this series described the distribution of three bacterial polysaccharides among the cells of the mouse after intravenous injection In this article Albert H Coons Elizabeth H Leduc and Melvin H Kaplan (Harvard Univ) report the results of similar studies with crystalline egg albumin crystalline bovine albumin and human gamma globulin The studies were carried out by taking advantage of the fact that the antibody molecule retains its specificity after conjugation under gentle conditions with aromatic compounds through the azo and the carbamido linkages This permits the use of antibody coupled with fluorescein isocyanate as a specific stain or fluorochrome which deposits an immune precipitate over those areas of a tissue section containing the homologous antigen The precipitate is brightly fluorescent under the fluorescence microscope and indicates presence of the antigen

Results confirmed those of the previous studies with regard to the function of the reticuloendothelial system in taking up antigenic material in solution In addition they extended the previous observations on distribution of acid bacterial polysaccharides to three proteins of differing molecular weight After intravenous injection both types of foreign materials

(7) J E p M d. 93 173 188 F bru ry 1951

were found in the vascular endothelium in connective tissue cells and adsorbed on collagen fibers in lymphoid cells and in the epithelium of the adrenal cortex kidney and liver Although their rates of disappearance differ greatly both remain longest in the reticuloendothelium and connective tissue

The most unexpected finding was the presence of each protein in the nuclei of the cell types previously mentioned Nuclei of liver and kidney cells particularly contained antigen in higher concentrations than cytoplasm and more often antigen when none was detectable in cytoplasm By means of photographic records under the fluorescence microscope of sections stained for antigen and direct observation under the light microscope of the same field subsequently stained with hematoxylin and eosin it was determined that the antigen was not adsorbed to chromatin or nucleoli but was apparently in solution in the nuclear sap

The theory has been advanced that the presence of antigenic material in an antibody producing cell modifies the synthesis of globulin in a way which can be transmitted to its descendants to account for the continuing production of antibody after the antigen has disappeared and for the difference between the first and subsequent doses of antigen The finding of antigen in the nucleus indirectly supports this theory

In serum disease the involvement of the connective tissue of the heart and vessels and of the glomeruli is evidently governed less by selective localization than by focal persistence the antigen must remain in those locations in high enough concentration and long enough for sufficient antibody production to take place This perhaps accounts for the massive doses of antigen required to elicit serum disease

[The authors are to be congratulated on development of a beautiful experimental technic This method should be applicable to many types of study not only in the fields of immunology and infectious disease but also in physiology and pathology —Ed]

Electron Micrographs of Newcastle Disease Virus Propagated in Cave Bat (Myotus Lucifugus) Reginald L Reagan Elizabeth J Smith and A L Brueckner[8] (Univ of Maryland) conducted electron microscope studies to determine the morphology of the Newcastle disease virus after intracerebral passage in Myotus lucifugus Various fields chosen for electron examination showed many virus particles with uniform

(8) J B t 61 37 40 J y 1951



F g 20 — \ w tl d f m b ain of nf t d b t, alt one beult mb yonated egg × 122,500 (Courte y f Reag R L et al J B ct 61 37 40 J y 1951)

tail structure Figure 20 shows typical tail forms apparently segmented from the first bat passage after virus cultivation in *embryonated eggs The high magnification brings out great* detail

[This is only one of a number of excellent electron microscope photographs of viruses that appeared during the last year —Ed.]

Relation of Herpes Virus to the Cell Nucleus The selectivity with which viruses tend to attack specific tissues and cells resulting in characteristic types of morphologic alterations invites investigation of the manner in which the virus *becomes attached to the cell Infection with the herpes sim*plex virus is typified by presence of inclusion bodies in the nucleus which have been thought by some investigators to

represent the localized virus In recent years centrifugation has been increasingly used to separate the structural units of cells Thomas Francis Jr and Hilda B Kurtz[9] (Univ of Michigan) thought therefore, that similar procedures could be used to determine whether herpes virus has a selective affinity for the nuclei of susceptible cells and to ascertain whether the virus is intimately related to the nucleoprotein of the nucleus

Although the inclusions produced by herpes virus are nuclear in location no evidence was obtained to indicate that herpes virus is selectively bound to nuclei or to nuclear nucleo protein Results indicate that the inclusions are *not* herpes virus

What Is Left of the Theory of Focal Infection In 1912 Billings championed the relation of chronic focal infection to arthritis and nephritis and thereby promptly popularized the view that an infection localized in one part of the body might be the focus from which by bacterial metastasis or through convection of bacterial products secondary disease might arise elsewhere in the body Application of the focal infection theory involved removal of all such foci in prophylaxis and treatment of the diseases they were supposed to cause In the next two decades enthusiasm for the theory far exceeded any evidence or reason for its validity However in the last 10 years clinical failures and much negative evidence have been reported by disbelievers in the theory Many authors would end the title of this article with a question mark instead of a period and would answer the question Nothing Never theless Richard A Kern[1] (Temple Univ) believes that some thing does remain of the concept and that it deserves to be restated

The glaring weaknesses of the practice of the focal infec tion theory were calling any structure as well as any lesion containing bacteria a focus assigning to the focus an etiologic role in any disease that happened to coexist in the patient deciding that every possible focus must be removed even though the possessor was in no way ill and the thera peutic excesses committed in the name of the theory

This mass of fallacy and unwise practice unfortunately

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(9) Yal J B ol & M d 2 579 587 J ly 1950
(1) M Cl n No th Am ca 34 1 05 171 No embe 1950

obscured certain established facts that then existed and still exist (1) A boil on the back of the neck is at times followed by a perinephric abscess and the organism isolated from the abscess is of the same strain as that found in the boil This is an example of an acute focus of infection (2) Gonococcic infection of the urethra may be followed by gonococcic arthritis (3) There are undoubted cases in which bacterial endocarditis due to Streptococcus viridans has been traceable to a dental infection cases in which the same strain of streptococcus is recovered from the blood and from the root of an infected tooth and cases in which cure has been effected but the disease recurs months or years later immediately after tooth extraction (4) Many cases of arthritis and of disease of the uveal tract of the eye have occurred in which there was an apparent relation to a dental focus of infection removal of which was followed by cure

In all these examples it is significant that the focus is one in which mechanical factors favor recurrent production of bacteremia the 120 200 lb of pressure which the jaw muscles are capable of exerting the compression of the tonsils during swallowing the frequent stresses on the prostate But more important than the mere presence of a focus of infection and of mechanical factors that act on the focus are conditioning factors that render the patient vulnerable to minimal bacteremic episodes or that by lowering his defensive powers increase the degree of such bacteremia Conditioning factors will result in secondary disease far more readily when a focus of infection exists than if there is no such focus The focus can therefore not be ignored Conditioning factors include a damaged heart valve a traumatized joint cartilage fatigue exposure mental depression fear malnutrition avitaminosis and anemia

In the light of these observations there are numerous practical considerations in the management of foci of infection Whatever else of good or bad came out of the early abuses of the focal infection theory a tremendous stimulus resulted for better dentistry Relatively few types of foci are important as causes of distant disease Dental tonsillar and prostatic foci comprise the great majority of those of major significance Recognition of an active focus in the prostate or even the tonsils is easy but recognition of an active dental

focus is not simple A focus of infection when found deserves treatment not on the remote chance of preventing trouble at a distant site but to clean up an abnormality The commonest diseases in which a focus of infection should be considered are infectious arthritis iritis iridocyclitis bacterial endocarditis acute glomerulonephritis myositis and neuritis In diseases in which focal infection is not a likely factor but the focus exerts a detrimental effect on the patient s general health it should be removed with the full understanding that the disease itself will not be influenced Though removal of a focus may have an unfavorable effect on an existing disease this danger can largely be obviated by use of an antibiotic

Cultural Properties and Pathogenicity of Certain Microorganisms Obtained from Various Proliferative and Neoplastic Diseases are discussed by Virginia Wuerthele Caspe Eleanor Alexander Jackson, John A Anderson James Hillier Roy M Allen and Lawrence W Smith[2] (Rutgers Univ) The original cultures isolated on Petragnani and Lowenstein egg mediums from blood and lesions of patients with scleroderma revealed acid fast granules of various sizes and rodlike forms These scleroderma strains have produced a consistent type of lesion when inoculated into white mice With the technic developed in the scleroderma study similar micro organisms were isolated from the blood of 18 cancer patients 7 of whom had Hodgkin s disease by inoculating their blood into chick embryos So far no growth has been obtained from a control series of 17 normal *persons Concomitant with the study* of isolates obtained from human cancer isolations were also made repeatedly from Rous chicken sarcoma and mouse sarcoma 180

These organisms which appeared primarily as small acid fast granules in young cultures and which tended to become non acid fast in the larger forms present in old cultures exhibited a number of types such as (*a*) minute filtrable granules beyond the limits of visibility of the light microscope (*b*) larger granules approximately the size of ordinary cocci readily seen with the light microscope (*c*) later globoid forms (*d*) rodlike forms with irregular staining and (*e*) occasionally globoid forms which appeared to undergo polar

(2) Am. J M S 220 638 648 D mbe 1950

buddmg Cultures moculated into experimental animals pro duced a characteristic pseudocaseous lesion Huge numbers of lymphocytes appeared as part of the response

Final classification of these organisms cannot be made at this time That they may represent isolated instances of a group of biologically related organisms capable of causing proliferation in the host is not overlooked Whether these organisms are of primary or secondary significance in de velopment of malignant disease remains to be established

[I really am skeptical —Ed]

THE CHEST

J BURNS AMBERSON M.D

PART II

THE CHEST

PHYSIOLOGIC MECHANISMS

Arteriovenous Shunts in Human Lung were studied by Charles E Tobin and Manuel O Zariquiey[1] (Univ of Rochester)

METHOD — At autopsy fresh lungs were obtained from persons with little or no respiratory disease They were gradually inflated with compressed air to about normal size and then allowed to deflate Glass cannulas were ligated in the hilar ends of the pulmonary artery and veins Normal saline solution was perfused at a pressure of 30-40 mm Hg into the pulmonary artery to wash out residual blood Several hundred small glass spheres 10 750 μ in diameter were then washed into the pulmonary artery with 50 100 cc saline solution Perfusion was continued and glass spheres collected from the venous cannulas Solutions of liquid latex or vinyl acetate were injected into the pulmonary vessels In six instances radiopaque mediums were added to the injection mass

Spheres up to 500 μ in diameter were washed through the pulmonary veins of nine adult and two neonatal lungs by the saline perfusion An average of 37 5 spheres were recovered from each lung No spheres were recovered from the perfusate of the other 12 lungs

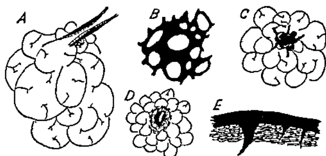
X rays of the lungs injected with radiopaque mediums and study of latex or vinyl acetate injected specimens showed that *no arteriovenous shunts were present in the hilar region* or along the course of the larger branches of the pulmonary artery and vein At the apex of the lobular division of the bronchial pulmonary segments shunts up to 500 μ in diameter were found Shunts 50 100 μ in diameter were located at the level of the smaller bronchi and respiratory bronchioles and shunts 20 25 μ in diameter near the alveolar sacs and alveoli Shunts up to 200 μ in diameter were also found in the pleura

[This is a most interesting demonstration The physiologic value of these shunts will arouse speculation and study —Ed]

(1) Proc. Soc. Exper. Biol. & Med. 75 827 829 December 1950

Patterns of Pulmonary Fibrosis as Related to Pulmonary Function Because discrepancies are often noted between de gree of lung involvement shown by x rays and severity of subjective symptoms David M Spain[2] (Columbia Univ) studied autopsy material from a great variety of pulmonary conditions Pattern and distribution of fibrosis in the lungs rather than degree of fibrosis were found to be more closely related to severity of both objective and subjective clinical manifestations Fibrosis could be divided into bronchial in terstitial parenchymal vascular and pleural types (Fig 21)

The bronchial tree may be involved by any type of in flammation and fibrous tissue may be deposited in or around



F g 21 —*A* b n h l fib w th b t t e mpby ma *B* t t tal fibros s *C* intra alveolar (p en hym l) fibros s w th surround ng d st t n mphy s m *D* rt n l r l *E* pleu al fib w th c mp e on of l g (C rt sy of Sp n D M Ann Int M d 33 1150 1163 N mbe 1950)

the walls of bronchioles This either narrows the lumen or imparts a rigidity to the wall The main sequela of this type of fibrosis is obstructive emphysema The amount of ob structive emphysema depends on extent and duration of the inflammatory process The physiologic disturbance which re sults is essentially ventilatory in character and its main fea tures are decreased vital capacity and increased residual air Such alterations may be seen in tuberculosis silicosis and Boeck s sarcoid

Pure diffuse fibrosis of interstitial tissues of the alveolar septa is rare It may result from virus infection scleroderma or beryllium intoxication Functional changes are directly re lated to thickening of the alveolar wall and separation of the capillaries in the septa from the alveolar interspace by inflam

( ) A n I t Med 33 1150 1163 N mb 1950

mation edema and fibrous tissue The disturbance is essentially respiratory in nature There is interference with the diffusion of carbon dioxide and oxygen and the resulting anoxia may specifically injure the myocardium The condition is often associated with subintimal fibrous proliferation in the smaller arterioles

Intra alveolar fibrosis of the parenchyma is probably the commonest type of pulmonary fibrosis The amount of parenchyma involved may vary widely Tuberculosis suppurative pneumonia Friedlander s bacillus pneumonia pneumonia secondary to inhalation of foreign lipoid or fibrosis after radiation are some underlying causes An unqualified diagnosis is almost never justified for careful clinical investigation or postmortem examination usually demonstrates a specific cause Fibrous tissue involves the area to such an extent that it is no longer a functioning unit An important associated secondary change is distention emphysema in adjacent parenchyma Functional disturbances are directly proportional to amount of lung tissue involved and degree of distention edema

Fibrosis of the pulmonary vascular bed may result from multiple pulmonary arteriolar emboli with organization and canalization schistosomiasis of pulmonary vessels primary pulmonary arteriolar sclerosis endolymphatic carcinomatosis periarteritis of pulmonary vessels or congenital heart disease especially that associated with an exceptionally large volume of blood flow through a patent ductus Similar changes are seen in the lungs of patients with long standing chronic passive congestion secondary to mitral stenosis The commonest form of sclerosis involving pulmonary arterioles is that secondary to pulmonary hypertension The latter is most often associated with diffuse obstructive emphysema

Fibrosis of the pleura may result from organization of exudate which develops secondary to pyogenic empyema tuberculous empyema or trauma with blood in the pleural space Both ventilatory capacity of the lung and blood flow through the involved area are limited A secondary effect is development of distention emphysema in the uninvolved portions

Study of the causes of cor pulmonale in 100 cases in which autopsy was done showed that fibrosis of the vascular bed is rarely a direct cause of pulmonary hypertension Emphy

sema bronchiectasis bronchial asthma tuberculosis and sili cosis are responsible for about 80 per cent of cases The fibrous tissue primarily involves the bronchial walls and it is through the resultant emphysema that cor pulmonale develops

[The pattern of pulmonary fibrosis can sometimes be judged approxi mately by clinical and x ray examination provided the underlying pathol ogy as explained by Spain is visualized This of course is of funda mental importance in prognosis and treatment—Ed]

Pulmonary Fibrosis and Respiratory Function George W Wright and Giles F Filley[3] (Trudeau Found) point out that determination of the influence of pulmonary fibrosis on the respiratory apparatus is difficult because of the uncertain na ture and location of the pathologic process the frequent co existence of other pathologic conditions and the statistically determined and widely variable normal data with which physiologic observations must be compared

A priori considerations suggest that fibrosis may produce respiratory and circulatory disturbances in several ways Re duction of total lung volume and of maximal breathing ca pacity may result from encroachment on the air spaces or on the distensible or canalicular parts of the thoracic apparatus Decrease in alveolar ventilation can be caused by airway obstruction and will result in an abnormally high partial pres sure of alveolar CO and a low pO This hypoventilation of diseased areas may be compensated for by the shunting of blood away from these areas and by hyperventilation of other areas The mechanism of shunting is not clear Proliferation of the connective tissue that supports the alveolar vascular bed may impede diffusion of oxygen into the alveolar capil laries This defect may also be somewhat compensated for by the shunting of blood away from diseased areas The restric tion or obliteration of the vascular bed which fibrosis may cause results not only in pulmonary arterial hypertension and its sequelae but also in reduction of the area available for dif fusion Abnormal respiratory stimuli may arise from areas of fibrosis and cause hyperventilation

The various aspects of pulmonary function were measured in nine cases which were selected because they represented for the most part a single pattern or known combinations of patterns of connective tissue proliferation

In Case 1 that of a boy with extensive cavitary tubercu

(3) Am J Med. 10 642 661 May 1951

losis of the left upper lobe physiologic studies showed reduction in all lung volumes reduced maximal breathing capacity larger than normal minute ventilation and normal alveolar blood gas relationships at rest and during exercise This last finding and a reduction in oxygen uptake on the diseased side indicate the shunting of blood away from the diseased area The only physiologic abnormality found in a man with widespread nodular pulmonary lesions of Boeck s sarcoid (Case 2) was pronounced overbreathing on the most severe exercise As in Case 1 this hyperventilation was believed to arise from abnormal intrapulmonary stimuli

No abnormal physiologic findings were present in a man with discrete nodular silicosis of many years duration (Case 3) Two patients with conglomerate silicosis (Cases 4 and 5) had somewhat contrasting physiologic findings In Case 4 lung volume was normal and there was no evidence of emphysema Slight arterial hypoxia was present In contrast evidence of emphysema a much lower maximal breathing capacity and a greatly lowered work capacity were present in Case 5 The differences between these two may be due to a difference in extent and duration of fibrosis or in distribution of the fibrotic process In such cases there is evidence that bronchial obstruction is a more important mechanism in causing emphysema than overdistention from contraction of fibrous tissue

Severe physiologic pulmonary emphysema was present in a man with extensive bilateral fibroid tuberculosis of 27 years duration (Case 6) This case illustrates the severe emphysema which may result from such a fibrotic process In Case 7 that of a man with cavitary tuberculosis of limited extent but complicated by diffuse bronchial obstruction in the right lung from widespread bronchial fibrosis and inflammation increased residual air ineffective pulmonary rinsing lowered maximal breathing capacity and arterial hypoxia were found There was evidence that blood was shunted away from the diseased lung

In a man with the pulmonary granulomatosis of beryllium workers (Case 8) physiologic studies showed evidence of a barrier to diffusion of oxygen and carbon dioxide into the pulmonary capillary blood

Studies were made before and after pleural decortication

sema bronchiectasis bronchial asthma tuberculosis and silicosis are responsible for about 80 per cent of cases The fibrous tissue primarily involves the bronchial walls and it is through the resultant emphysema that cor pulmonale develops

[The pattern of pulmonary fibrosis can sometimes be judged approximately by clinical and x ray examination provided the underlying pathology as explained by Spain is visualized This of course is of fundamental importance in prognosis and treatment —Ed.]

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(3) Am J Med. 10 642-661 M y 1951

cent had consistently lower collateral flow values than the second group of three whose resting arterial blood oxygen saturation was above 85 per cent The relation between arterial oxygen saturation and collateral flow may be a measure of the benefit the patient obtains from the anastomoses between sys temic and pulmonary arteries The large volume of collateral flow the burden of which is borne by the left cardiac ven tricle may be a cause of the left ventricular hypertrophy often observed in cor pulmonale

Collateral Respiration in Normal and Diseased Lung is discussed by Gustaf E Lindskog[5] Results of in vitro and in vivo experiments on human and animal lungs done with other observers led to the conclusion that pulmonary lobules are not functionally end organs from the standpoint of ventila tion It was further demonstrated that after the direct bron chial route is obstructed artificially an indirect and peripheral route for exchange of air and maintenance of inflation from adjacent directly ventilated segments exists This phenomenon was called collateral respiration It lessens the incidence of obstructive atelectasis equalizes pressure changes in the lung and tends to equalize alveolar gas tension of oxygen and car bon dioxide thus promoting a more uniform oxygenation of the venous blood

Collateral respiration is not dependent on the integrity of the circulation because it has occurred in excised lung and in living lung after the pulmonary artery has been ligated Aqueous solutions of dye may be easily passed from one pul monary segment to its neighbor by physiologic degrees of pressure thus indicating that the route for such exchange lies in anatomic defects of the alveolar walls such as might be represented by the pores of Kohn By attaching small water manometers the pressure necessary to actuate the peripheral natural pathways in vivo was found to vary between 1 and 1 5 cm (water)

Bronchoscopic suction in postoperative atelectasis is an effective therapeutic measure although it is unlikely that all of the secretions in the smaller peripheral bronchi are cleared The larger proximal and segmental branches are opened up so that collateral ventilation can deliver air to still obstructed segments By building up tidal and reserve air beyond the

(5) Y 1 J B 1 & M d 23 311 316 F bru ry 1951

on a young man with hemopneumothorax which subsequently became empyematous (Case 9) Before decortication there were a reduction in total lung volume and maximal breathing capacity a tendency to overbreathing during exercise and evidence of reduced blood flow to the injured side These defects disappeared after decortication This case illustrates the changes which extraparenchymal fibrosis may produce

The authors concluded that all alterations of pulmonary function from fibrosis anticipated by a priori considerations may occur but that there is no specific or uniform pattern of pulmonary dysfunction Unless fibrosis is complicated by diffuse emphysema or the majority of the alveoli are involved pulmonary fibrosis is a relatively benign process

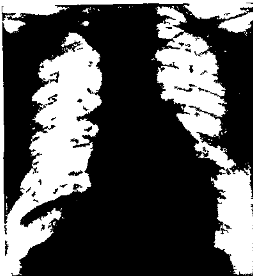
[This study demonstrates the complexity of the functional effects of pulmonary fibrosis and the importance of careful judgment in evaluating disability due to this cause In a good many cases in which such pulmonary damage has occurred disability is precipitated or aggravated by superimposed infection causing bronchitis or bronchopneumonia The problem then is to clear up the infection if possible—Ed]

Circulatory Changes in Chronic Pulmonary Disease Study of Pulmonary Collateral Circulation Frank D Gray Jr Paul R Lurie and Ruth Whittemore[4] studied 10 patients with some type of chronic pulmonary disease The outstanding symptom was disabling dyspnea Three had frank left ventricular failure All but two had distended neck veins All but three revealed a right to left shunt through inadequately aerated tissue

In seven patients presence of collateral flow could be determined by cardiac catheterization Since there was no increased pressure gradient collateral flow was attributed largely to chronic inflammation Anoxemia probably did not stimulate development of the abnormal channels because correlation between collateral flow volumes and arterial saturation was insignificant

In the seven patients mixed venous blood was being shunted through nonaerated pulmonary capillaries which served as collateral channels between bronchial and pulmonary arteries In all volume of collateral flow required to affect favorably the blood oxygen saturation was excessively large These patients could be divided into two groups four whose resting arterial oxygen saturation fell below 85 per

(4) Yale J Biol & Med 23 380 389 Apr 1951





F g 22 (top) —Doubl po film n normal bj ct h w g l g f d phr gm nd w de b mo me t

F g 23 (bottom) —Larg on f d ph gm d b t b m m t nkyl g p dyl t

(Co t y f H t F D t l A Rh m t. D 9 116 131 J 1950)

obstruction the cough mechanisms may again become effective

Within the past two years existence of collateral respiration in the living human has been verified by appropriate cannulation The evidence now seems complete in both man and lower animals for a peripheral pulmonary mechanism which provides an alternate and indirect route for air transport when the direct channels of a lobule or segmental group are obstructed

Thorax in Ankylosing Spondylitis F Dudley Hart Andrew Bogdanovitch and W D Nichol[6] (Westminster Hosp London) reviewing 65 cases noted exertional dyspnea unlike that in cardiac or pulmonary disease with difficulty in moving the chest wall and tightness in the ribs and thoracic cage muscles especially anteriorly but also in the flanks The chest aches feels stiff and immobile and cannot be filled satisfactorily on deep inspiration Bronchial spasm is absent and cough rare

Measurement showed that in about half the cases thorax expansion at the nipple level was 1 in or less and 27 patients had vital capacity below 75 per cent Rib sternal intercostal or thorax joint tenderness was sometimes present

X ray changes appear first in posterior intervertebral articulations and costotransverse and costovertebral joints and later in the vertebral body and sternoclavicular and manubriosternal joints Routine anteroposterior x rays show many of the costovertebral joints reasonably well Other joints may be visualized on oblique views depending on the angles at which these joints lie Articular margins lose their sharp outlines because of irregular osteoporosis and joint spaces are narrowed because of destruction of the articular cartilages The final stage is complete bony ankylosis Fluoroscopy reveals full movement of the diaphragm on deep respiration and diminished or sometimes absent movement of the ribs To record these changes a double exposure technic has been adopted The patient lies supine on the film and during full inspiration one third of the normal exposure of the chest is made he then exhales completely and the remaining two thirds of the exposure is made on the same *film The resulting film shows* the excursion of the diaphragm and movement of the ribs

(6) A n Rheum t. D s. 9 116-131 J e 1950

by a tidal volume only slightly greater than the physiologic dead space or by insufflation pressure that just exceeds the elastic recoil of the lungs Reoxygenation of the failing organism is the fundamental mechanism of resuscitation by artificial respiration Oxygen alone accomplishes this objective It is probable that the fundamental aim of artificial respiration *is to reoxygenate a failing heart* This generality may be applied only to fulminating anoxia because in other types the aim of resuscitation may be to restore a circulation that has already failed or to prevent an anoxic cerebral insult

Respiratory recovery could not be produced by insufflation of very pure nitrogen Recoveries reported by other investigators may be due to contamination of commercial nitrogen gas (guaranteed to be 99 7 per cent pure or better) with considerable amounts of oxygen

Breath Holding Test in Pulmonary Insufficiency Evaluation of 1,000 Studies Edward A Gaensler Donald F Rayl and Dorothy M Donnelly[8] (Harvard Univ) studied 425 patients about half of whom had pulmonary tuberculosis with complications and had received collapse therapy Breath holding was not closely related to maximal breathing capacity vital capacity or subjective dyspnea The training factor of breath holding capacity was 12 times as great as that of vital capacity and 5 times larger than that found with repeated performance of the maximal breathing capacity test The psychologic factor was large indicated by the fact that when patients observed the stop watch or were deceived about correct time intervals breath holding time could be more than doubled Variations in breath holding time in the same patient were so large from day to day that the test was considered undependable for evaluation of pulmonary function Therefore it is recommended that its use be abandoned

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DIAGNOSTIC AND THERAPEUTIC PROCEDURES

Acute Suppurative Bronchitis and Bronchiolitis in Chronic Pulmonary Disease Diagnosis and Management Leonard Cardon Louis Lemberg and Regina S Greenebaum[9] state

(8) S g Gy ec & Ob t 92 81 90 J ry 1951
(9) A J t M d 34 559 591 M h 1951

the elevation of the sternum is shown by the movement of sternal ends of the clavicles (Fig 22) With extensive involvement of the costovertebral and costotransverse joints there is often complete absence of movement of the ribs but full movement of the diaphragm (Fig 23) Generalized osteoporosis is sometimes found in acute cases Ossification of various ligaments is usually a late feature Bony erosions and periosteal thickening at muscular attachments may be observed

The most important factors in therapy are full mobility as early as possible avoidance of the prolonged rest and immobilization which has been the treatment in the past early active breathing exercises and maximal freedom of movement to allow free use of the lungs In acute episodes extreme thoracic stiffness and pain may exclude full mobility however after about two weeks of deep x ray therapy breathing and body exercises usually may be started As soon as rib movement becomes less painful and thoracic expansion improves the patient is encouraged to enjoy maximal freedom of movement Surgical treatment in the form of spinal osteotomy is indicated when spinal kyphosis causes diminution in diaphragmatic excursion

[These are interesting suggestions for the detection and asse ment of this condition The possibility of helping these patients on the basis of a rational understanding of the mechanisms involved seems promi ing although the duration of the benefit remains to be determined—Ed.]

Requirements for Resuscitation by Artificial Respiration in Fulminating Anoxia M Brucer and H G Swann[7] (Univ of Texas) gave dogs pure nitrogen to breathe and when they were unconscious from anoxia inserted a cannula in the femoral artery When the systolic pressure fell to about 105 mm various resuscitating maneuvers were applied

Minimal requirements for resuscitation by artificial respiration were (1) a single insufflation of the lungs to the full vital capacity with pure oxygen (2) periodic insufflation with a gas mixture containing 2 per cent oxygen or more (3) periodic insufflation with a tidal volume of at least 4 cc air/kg body weight or (4) periodic insufflation at an insufflation pressure of 3 7 mm Hg

The anoxic dog needs only a small amount of oxygen to restore its circulation and breathing This amount may be furnished by gas mixtures extremely low in oxygen content

(7) J Appl Phy l 3 479 488 F bru ry 1951

and glottis locally before aspiration is attempted If catheter aspiration is impossible the aid of an otolaryngologist or an anesthesiologist should be enlisted A stiff Magill tube may be passed and catheter aspiration performed through it If these procedures are ineffectual tracheotomy may facilitate removal of secretions

Bronchodilators and vasoconstrictors are administered to shrink the bronchial mucosa and dilate the bronchi to maintain as wide and patent an airway as possible Aqueous solutions of epinephrine 0 5 1 cc of 1 per cent concentration or 1 cc of 1 per cent neo synephrine ® or mixtures of these may be placed in a nebulizer and administered as an aerosol mist through the mouth or tracheotomy tube every two to four hours The mist is produced by passing an oxygen stream from a separate tank flowing at 4 L /minute through the nebulizer Aminophylline or ammonium chloride solutions may also be administered in this way Epinephrine in 1 1 000 aqueous solution 0 2 0 6 cc or ephedrine sulfate 0 025 0 05 Gm may be given for the same purpose Epinephrine in oil given subcutaneously acts for a longer time but must be used with caution Aminophylline 0 24-0 48 Gm may be given intramuscularly intravenously undiluted or by slow drip diluted in 1 L of 5 per cent glucose in normal saline or distilled water It is also effective when given as a rectal suppository in 0 5 Gm dosage

Antibiotics and chemotherapy are given to overcome the acute infection The specific agent is determined by sensitivity tests on organisms cultured bacteriologically These agents may be administered by aerosol and/or parenteral routes Sodium or potassium iodide is the most effective expectorant Sedatives may be necessary for the restless patient but morphine is usually contraindicated when medullary centers are depressed When a patent airway and adequate oxygenation have been attained the restless patient may be given 2 5 mg morphine Demerol ® in doses of 25 50 mg may be preferable to morphine When stimulants are required the most effective are caffeine sodium benzoate 0 48 Gm subcutaneously intramuscularly or intravenously coramine ® 3 5 cc of 25 per cent solution intravenously or metrazol ® 1 3 cc intravenously Air filters and air conditioned rooms are of value if asthma due to inhalants is a prominent part of the clinical picture

that an episode of acute bronchitis superimposed on chronic asthmatic bronchitis emphysema pulmonary fibrosis or bronchiectasis may so obstruct the bronchi that an acute respiratory emergency and death by suffocation may be precipitated

The clinical picture is characteristic The patient is usually past middle age and has had one of the aforementioned chronic pulmonary diseases for a number of years An acute upper respiratory tract infection develops which travels downward to produce acute tracheitis and bronchitis In most instances the acute infection subsides uneventfully but in a few it becomes progressively worse and leads to narrowing of the bronchi and occlusion by accumulated secretions Dyspnea increases cough becomes more severe and there are tachycardia and cyanosis As anoxemia increases anxiety restlessness and apprehension follow Finally disorientation and delirium are followed by stupor and coma with asphyxial depression of the brain Death may occur in 12 hours to 3 days after onset The condition is often misdiagnosed as acute left ventricular failure or pneumonia

Immediate aims of treatment are restoration of adequate oxygenation and opening and maintenance of a clear airway Highly desirable but not always possible is prevention of acute upper respiratory infection The potentialities of such infections demand that they be treated seriously from the beginning

The most urgent necessity in severe cases is administration of oxygen in concentrations as near 100 per cent as possible It is best administered by the Barach Eckman or B L B oral nasal mask With clinical improvement the concentration may be lowered when it is less than 50 per cent administration by nasal catheter or tent may be substituted The oxygen must be adequately humidified

Mechanical aspiration of accumulating tracheal and bronchial secretions is the second urgent measure if the cough reflex is weak or absent sensorium is depressed or the patient is stuporous or in coma Many times catheter aspiration of the trachea is satisfactory and may be done as often as necessary The catheter should be connected to a vacuum bottle of an electric suction machine If glottic spasm is severe and a reaction results it is advisable to anesthetize the pharynx

cious di charges Opiates and other drugs which depress respiration should be used with extreme caution since they have been known at times to have fatal effects —Ed]

Effect of ACTH in Chronic Lung Disease Study of Five Patients is presented by Morton Galdston Shirley Weisenfeld Bry Benjamin and Milton B Rosenbluth[1] (New York City) A man 50 with no history or signs of cardiac strain but with advanced pulmonary emphysema fibrosis moderately de formed thoracic cage seasonal asthma for 18 years and status asthmaticus for 2 years had dramatic response to ACTH within 2 days after beginning treatment he had a feeling of well being bordering on euphoria and showed prompt im provement in pulmonary function as demonstrated by objec tive study When ACTH was discontinued there was prompt regression to the previous state

In another man 50 with striking thoracic cage deformity who had had year round asthma since childhood compli cated by advanced pulmonary fibrosis emphysema cor pul monale and congestive heart failure ACTH administration resulted in fluid retention which taxed the diminished cardiac reserve

A patient with proved Boeck s sarcoid had a dramatic re sponse to ACTH characterized by defervescence disappear ance of stiffness swelling of joints and subcutaneous and eyelid nodules and healing of an indurated ulcer resulting from Kveim antigen Impaired pulmonary function showed improvement but x rays did not demonstrate shrinkage of enlarged hilar lymph nodes When ACTH was discontinued clinical signs of activity of Boeck s sarcoid recurred mental depression increased and suicide followed

In a patient with chronic bronchiectasis fibrosis and em physema subsequent to arrested bilateral upper lobe tuberculosis ACTH caused some subjective improvement but neither beneficial nor deleterious effects after seven weeks of therapy A fifth patient with pulmonary emphysema secondary to changes with age had respiratory distress and dependent edema during administration of ACTH

Liquefaction of Viscous Purulent Exudates by Deoxyribo nuclease John B Armstrong and J C White (Postgradu ate Med School of London) obtained the enzyme from ox

(1) Am J M d 10 166 181 F b y 1951
( ) L nc t 2 739 74 D 9 1950

Fluid balance and nutrition must be maintained in the as phyxiated and restless patient who cannot eat or drink ade quately When fluids are being administered parenterally the tendency to pulmonary edema must be kept in mind con stantly An amount of fluid sufficient to maintain a 24 hour urinary output of 1 000 1 500 cc should be given Serum, plasma or blood usually is not indicated The high incidence of chronic cor pulmonale in these patients with the likelihood of development of right heart failure should temper any tendency to overload the venous circulation with intravenous infusions Venesection is indicated when progressive cyanosis is associated with rapidly increasing venous pressure Re moval of 500 750 cc blood temporarily improves the coronary circulation and may prolong life until restoration of the air way adequate oxygenation and rapid digitalization improve cardiac function and tissue respiration Rest and quiet are essential Treatment and medication should be planned to produce minimal disturbance Intelligent and capable special nurses are essential However the patient requires constant attention of the attending physician or a capable assistant day and night

Certain complications may be fatal unless anticipated recognized rapidly and effectively treated Small pleural ef fusions may critically reduce the vital capacity and result in death unless aspiration is done thoroughly and early Ten sion pneumothorax calls for immediate insertion of a needle into the involved region If conservative measures do not re lieve massive atelectasis bronchoscopic aspiration is required Reflex ileus of the stomach or bowel requires gastric aspira tion and Wangensteen suction Fecal impaction should be pre vented by oil retention and cleansing enemas as necessary The retention catheter must be used for acute urinary reten tion Phlebothrombosis in the lower extremities may be pre vented by passive exercises Anticoagulants should be used only when thrombosis or embolism is apparent Although the various medications enumerated may be lifesaving reactions to these drugs remain a constant danger

[The obstructive mechanisms occurring in these bronchopulmonary conditions are observed frequently Clinical judgment must be u ed in determining the presence and nature of the obstruction and in selecting the most practical and feasible means for relief In some cases simple steam inhalations properly administered help liquefy and expel the tena

pancreas and prepared solutions containing 0 05-0 5 mg /ml in M/50 $MgCl_2$ with 1 per cent gelatin The higher concentrations proved most satisfactory clinically Solutions were sprayed directly into the mouths of seven patients through a 3 in glass tube about 1 in in diameter Flow of 6 8 L /minute of 5 per cent carbon dioxide and 95 per cent oxygen was supplied through a T tube The other wing of the T was closed by the patient s thumb during inspiration and opened during expiration The spray was administered once only or three times a day for two or more days to a maximum of 11 inhalations Deoxyribonuclease was not inhibited by penicillin or streptomycin

Figures 24 and 25 compare the appearance of purulent sputum with that of mucinous nonpurulent sputum When such specimens are treated with the enzyme the Feulgen positive reaction of the fibrils almost disappears but the nuclei of many intact leukocytes retain their staining characteristics After incubation viscosity of the enzyme treated sputum may be greatly reduced

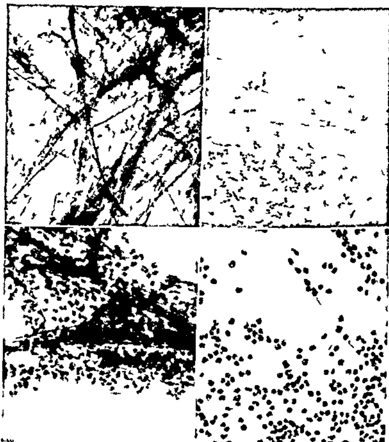
Two bronchiectatic patients used the enzyme in a concentration of 0 5 mg /ml dosage being 10 ml /day divided into three doses One patient with bronchiectasis of 13 years duration said that for the first time in 3 years he could walk up two flights of stairs without stopping he slept better breathed more easily on awakening and brought up sputum more readily Quantity of sputum increased the day after the first inhalation and thereafter decreased Cytochemical changes the day after the first inhalation are illustrated in Figures 26 and 27 Similar changes were observed in the second patient

No patient had a toxic or anaphylactic reaction

[Th s treatment seems to offer promi e in properly selected cases It is doubtful whether bronchial secretions of a tenacious mucoid character would be materially influenced —Ed]

Effects of Cortisone and ACTH in Cases of Chronic Pulmonary Disease with Impairment of Alveolar Capillary Diffusion John R West John H McClement Douglas Carroll Harry A Bliss Marvin Kuschner Dickinson W Richards Jr and Andre Cournand[3] (New York City) treated three patients The process was due to scleroderma in one to pulmonary granulomatosis of undetermined etiology in a second

(3) *Am J M d. 10 156 165 F b ry 1951*



F g 24 (t p left) —P ul nt putum (w t fi d n s sa s lut on) bow g Fe l g n po ti fib ls a a g d t nds a d ntangl g l kocytes (d d f om × 100)

F g 25 (t p right) —No p l nt mu p t m (wet fi ed n sa sol t o) show ng Feulg n s t n fi d to ucl i f l ukocytes wh ch e mbedded mucop t (d c d f m × 100)

F g 26 (bott m left) —Bef hal t on of nayme fo b ch ectasis Sputum hows leukocyt s nta gl d n th k pes f F lgen po ti e fib ls (d d f om × 00)

F g 27 (bottom ight) —O day fter nhal t n p y f 5 mg d o yr bo- l se Sp t m h w d t g at n and d appe nc of Feulgen pos ti e fb l w th r s tence of m ny f e l kocyt (d d f m × 200)

(Courte y of A m t g J B d Wh t J C L c t 2 739-742 D c 9 1950)

alveolar air and capillary blood as a result of a defective alveolar capillary membrane The major change in the patients who responded to treatment was reduction in volume of the physiologic venous admixture Oxygen diffusing capacity increased only moderately Reduction in physiologic venous admixture could have resulted from improved ventilation of certain inadequately ventilated alveoli rerouting of blood from capillaries in poor contact with alveolar air to



F g 29 (l ft) —C d pl dg of ght m ddl l b bef t m th ry b w g p lm a y pa nchyma filt ated by te l l l g a l m d d f m × 176

F g 30 (ght) —Ant m l l dg f ght m ddl l b fr r rt the p h g p l y t u n wh h g th l d ll ba b pl d by hy l li m t l el d f m × 18

(Cou t y f We t J R l Am J Med 10 156 165 F b y 1951)

those with better contact or improvement in diffusion of oxygen in certain areas where diffusion had been so greatly impaired as to increase physiologic venous admixture

The failure of therapy in the patient with scleroderma may be attributed to the dense collagenous and hyaline material in the alveolar septa which might be expected not to respond to cortisone In contrast the granulomatous process in the second patient would be more responsive to such treatment This contention is supported by biopsy specimens taken be

and to an unknown cause in the third Before treatment all had reduction in lung volume with relative preservation of maximal breathing capacity hyperventilation at rest or on exercise and arterial oxygen unsaturation at rest or after exercise All had reduced oxygen diffusing capacity in the lungs In two patients the physiologic dead space and the physiologic venous admixture increased significantly and there was pulmonary arterial hypertension at rest

Therapy caused no significant change in the pattern of

Fig 28 — Ch g in t g t lat nd a te al oxyg n sat rat n a so c t n w th ACTH and o t on therapy May 12 me em t made wh le pat ent b thed a r conta ng 25 pe nt oxyg n s b q ent m m ts mad wh le pat ent br ath d t g 21 per t o yg (oom) (Cou tesy of West, J R *et al* Am J Med 10 156 165 Feb uary 1951)

pulmonary dysfunction in the scleroderma patient but the others showed clinical improvement and betterment in some of the objective indexes of pulmonary function In the patient with pulmonary granulomatosis though there was no change in lung volume or maximal breathing capacity hyperventilation and arterial unsaturation were reduced In the third patient vital capacity and maximal breathing capacity were improved resting ventilation was reduced and resting arterial oxygen saturation was increased (Fig 28)

The fundamental basis for pulmonary insufficiency in these patients was impairment of gaseous exchange between

the results microscopic examination was made of material obtained by needle aspiration from the lungs of patients whose sputum contained lipophages or large amounts of free lipoids

Lipoid was found in 19 patients suspected of having lipoid pneumonia and in 2 controls Most of the patients had rheumatoid arthritis or central nervous system disease and all but two had used mineral oil or nose drops for long periods

The sputum of three patients contained only a few lipophages Abundant free sudan positive material was found in single droplets or cluster (Fig 31) These droplets were considered indicative of lipoid pneumonia since large drops are assumed to result from confluence of intracellular smaller droplets set free after disintegration of macrophages In 20 patients whose sputum contained lipoid material lung aspiration confirmed the diagnosis made from sputum Here the characteristic macrophages were single or arranged in clusters and occasionally were transformed into giant cells (Fig 32) Small or large extracellular lipoid droplets were sometimes noted

Relation of Particle Size to Inhalation Therapy with Micropulverized Penicillin Preparations George V Taplin Fred A Bryan Leonard Baurmash Warren W Greene Edward Hayes Walter Ralston and William Adolph[5] (Los Angeles) studied the effect of dried aerosols with particle sizes of 0 025 25 μ used in hermetically sealed inhalator cartridges with a powder chamber

Optimal particle size for local therapeutic action in infections of the lower bronchial tree was 0 5 5 μ Smaller particles were only partly retained larger ones did not penetrate the lung completely and were also deposited in the upper air passages where they were partially absorbed

After intranasal inhalation procaine penicillin micropowders were absorbed and excreted more slowly than sodium penicillin preparations More sodium penicillin was recoverable from urine after intranasal than after intraoral inhalation because there is greater absorption from the nasal mucosa and/or less destruction than occurs in the gastrointestinal tract After intratracheal insufflation absorption rates were as rapid and average blood level curves similar to those after intramuscular injection

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(5) A W t M d & S g 4 383 390 A g t 1950

fore and after treatment (Figs 29 and 30) which showed that epithelioid cells had been replaced by collagenous hya line like material The anatomic changes caused by therapy in the third case are unknown since biopsies were not done

Diagnosis of Lipoid Pneumonia by Examination of Sputum S Losner B W Volk W R Slade L Nathanson and M Jacobi[4] (Brooklyn) compared the sputum of 20 patients whose history and physical and x ray signs suggested

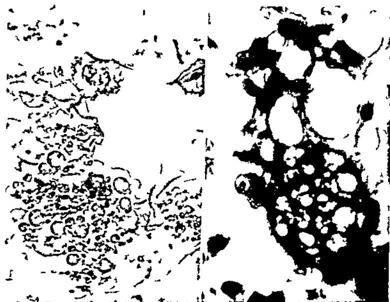


Fig 31 (left)—Lipoid in sputum ... partly free and partly ... macrophage Sudan IV, ... from × 300
Fig 32 (right)—... separated ... lipophage ... stained with sudan IV Wright's stain ... × 400
(Courtesy of Losner S et al Am J Clin Path 20 539 545 June 1950)

lipoid pneumonia with that of 45 controls All patients were placed on a fat free diet four to seven days before and throughout the period of examination Sputum was spread on slides and stained with sudan IV or Wright s stain Observations were considered positive if Wright s stain demonstrated characteristic vacuoles and macrophages and if similar vacuoles stained orange brown with sudan IV or if abundant extracellular fat staining material was noted To corroborate

(4) Am J Cl P th 0 539 545 J 1950

in nearly every instance masses of polymorphonuclear leukocytes being noted in the alveoli and interstitial tissues Pneumonia was rarer and milder when mouse serum was injected intrabronchially and the mice were allowed to inhale pneumococci for one hour

Microscopic study of the earliest phases of the pneumococcic pneumonia showed significant delay in the migration of polymorphonuclear leukocytes and macrophages into the



F 33 (ft) —I lm n. y I m] n d t fi fi day t l t H m t l d d f om 100
F g 34 (ght) —Ph gocyt f nly p f p mococ by l eol m ph ge f h fter t b h l ject f g m pe d d rum Eo n d m thylen tl d d f m × 1 00
(C rt y f H f d C G d H M J E p M d 91 45 60 M h 1950)

infected lung Macrophages already present in the normal lung engulfed pneumococci at a very slow rate (Fig 34) Although evaluation of phagocytosis in the lung with a viral lesion was more difficult comparable insufficiency of the phagocytic mechanism appeared to exist

Delay in polymorphonuclear leukocyte migration into the lung after injection of pneumococci increases susceptibility to infection since it allows ample time for the organisms to grow in the pulmonary fluid Support for this concept is found in the fact that patients with conditions complicated by

Complete pulmonary penetration was usually obtained in normal lungs whereas in lung tissue distal to an area of partial or complete bronchial obstruction much less penicillin was demonstrable These studies were carried out in lungs or lobes removed surgically When specimens of lung tissue were removed 12 14 hours after the last inhalation of penicillin the control blood sample taken simultaneously was likely to contain no penicillin but normal peripheral tissues contained 1 3 4 3 units/Gm

Acutely inflamed or irritated respiratory mucosa absorbs penicillin more rapidly and in larger amounts than normal mucosal surfaces Intranasal inhalation of micropulverized penicillin preparations usually has an effective topical action on the entire respiratory tract and also an appreciable systemic therapeutic effect The lung is probably a depot for inhaled penicillin releasing it gradually into the circulation

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PNEUMONIA

Pulmonary Edema in Influenzal Pneumonia of Mouse and Relation of Fluid in Lung to Inception of Pneumococcic Pneumonia Carl G Harford and Mary Hara[6] (Washington Univ) injected lethal or sublethal doses of influenza virus intrabronchially into mice Sections of the consolidated lungs prepared after five days showed viral pneumonia with pronounced pulmonary edema (Fig 33) To test the effect of pulmonary edema on susceptibility of mice to inhaled pneumococci sterile normal mouse serum was injected intrabronchially into mice and immediately after inoculation the animals inhaled fine droplets containing pneumococci for one hour The resulting increase in susceptibility to infection by inhaled pneumococci was due to growth of the pneumococci in the injected fluid Similar results occurred in pulmonary edema produced by alpha naphthyl thiourea

To determine whether bacterial pneumonia would result pneumococci suspended in normal mouse serum were injected intrabronchially into mice and sections of the lung prepared 24 hours later The lesion of bacterial pneumonia was present

(6) J E pe M d 91 245 60 March 1950

mal differential blood count Urinary findings were not un usual Extensive bacteriologic and other studies failed to reveal the causative agent X ray changes compatible with physical observations early in the course of the illness later (Fig 35) showed the extent of pulmonary infiltration far exceeding clinical manifestations The striking feature of the clinical course was the progressive increase of pulmonary in sufficiency evidenced by acceleration of pulse and respiratory



F g 36 (l ft) —O ganız d nd organizing al eol ex dat w th mall ne f m tapl tı b h l p th l m.
F g 37 (gbt) —N rv hbe l y l on w th t p l t nal cyt d bod (C rt y f T multy P A t *al* B ll J h H pk H p 88 239 63 M h 1951)

rates deepening cyanosis and intensified anxiety Fever was constantly present varying from 101 to 103 F Two patients had severe arthralgia without objective joint changes

Pulmonary changes at autopsy were similar in all cases All phases of an unusual pneumonia were seen Slightly older lesions undergoing early repair were present and other re gions showed extensive organized pneumonia Almost no nor mal lung tissue remained A viral rather than a bacterial origin was indicated by acute edema of the air spaces and interstitial tissues associated with fresh alveolar hemorrhages

pulmonary edema are known to be particularly susceptible to secondary bacterial pneumonia

[This study as well as others from the clinic of Dr Barry Wood, has greatly clarified the pathogenesis of pneumonias As indicated edema of the lung however produced seems to offer a favorable medium for bacterial growth and subsequent inflammation It may be said that compared with a physiologically moist lung a wet lung is more susceptible to pneumonia —Ed]

Peculiar Pneumonia Associated with Retinal Cytoid Bodies Philip A Tumulty Morgan Berthrong and A Mc Gehee Harvey[7] report three cases Persistent severe hacking



Fig 35 —S ft filt at n w th fl e t ar (C te y of T m lty P A et al Bull Joh Hopk n H p 88 39 63 Mar h 1951)

paroxysmal cough was a prominent early manifestation in two patients whereas a third had only occasional mild cough For several weeks two patients had constant low grade unexplained fever associated with progressive anorexia weight loss weakness headache and malaise One patient had pleural pain and a pleural friction rub was heard in another The principal physical alterations consisted of chest rales of varying character Typical cytoid bodies were observed in all patients on funduscopic examination A normal white blood cell count persisted throughout the illness of each with nor

(7) B U J h s Hopk s Hosp 88 239 63 M h 1951

Tuberculin Negative Tuberculosis, according to Willi Mascher[8] (Malmby Sweden) may be present after desensi tization during incubation when the infection has not taken (after BCG vaccination or natural infection) in cachexia in miliary spread of tuberculosis during the course of certain nontuberculous infectious diseases in reversion of pre viously tuberculin positive clinically healthy persons in bio logically healed tuberculosis in old age or in certain cases of active tuberculosis in which none of these conditions can be demonstrated

Of 196 tuberculin negative persons with questionable changes on mass miniature x rays 4 07 per cent had active tuberculosis The number of tuberculin reactors is no longer an absolute index of the number of persons infected with tuberculosis For practical purposes a negative tuberculin test in a case of suspected pulmonary disease does not exclude tuberculosis even if the patient is in good general condition and free from intercurrent nontuberculous infection In en vironmental examinations persons not reacting to tuberculin should be examined by x rays because it cannot be assumed with certainty that they are tuberculosis free Clinical or x ray evidence of tuberculosis must not be rejected because the tuberculin test is negative Though x ray changes were characteristic of pulmonary tuberculosis 11 patients failed to react to intradermal injection of 1 3 mg tuberculin In six patients Mycobacterium tuberculosis was isolated by sputum culture In two patients acid fast bacilli seen on microscopic sputum examination could not be isolated by culture In the other patients bacteriologic examinations for tubercle bacilli were negative Of six who were vaccinated with BCG two became tuberculin positive with a typical papule at the site of vaccination but the others remained negative Tests with codeine as a nonspecific irritant rate of absorption of a chlo ride wheal development of erythema after irradiation and incidence of passive dermographism demonstrated that the general reactive capacity of the skin was normal in all pa

(8) Am R T b 63 501 525 M y 1951

formation of fibrin plugs in alveoli hyaline alveolar membranes mild mononuclear cell reaction and lining of alveolar walls by plump elongated cells Of special interest was the widespread fibrous organization of pulmonary exudates associated with an acute process Organizing bronchiolitis and extensive metaplasia of bronchiolar and ductule epithelium (Fig 36) were associated with organized pneumonia in all cases

Cytoid bodies are white spots with fuzzy outline (Fig 38) generally one fifth the diameter of the optic disk they are usually seen only in the posterior portion of the retina



Fig 38 —Fundus oculi showing typical cytoid bodies and small hemorrhage (Courtesy of Tumulty P A [illegible] Bull Johns Hopkins Hosp 88 39 63 March 1951)

Though they have a characteristic histologic picture when viewed funduscopically they cannot be distinguished from other types of exudative lesions On microscopic examination the retinal nerve fiber layer is swollen and contains curious cell like bodies with a central eosinophilic globule (Fig 37) Since such bodies are seen in a wide variety of circumstances they are not typical of any particular disease entity

Although the cause of the illness is obscure an unusual localized form of collagen vascular disease with insidious onset progressing to pulmonary fibrosis cannot be excluded Other features point to a peculiar form of virus pneumonitis

[This study is of great interest because it is suspected that certain cases of pulmonary fibrosis are due to severe pneumonias which have resolved incompletely and gone on to organization —Ed]

residents reacted to the second dose in areas with high as well as low frequency of first dose reactors Frequencies of second dose reactors were more than twice as high in a large contiguous area east of New Mexico and south of Kansas Missouri Kentucky and Virginia which includes parts with very high moderate or low prevalence of first dose reactors The area showing the highest frequency of second dose reactors was centered in Louisiana and Mississippi with some indication of lower frequencies toward the east and west The proportion of second dose reactors was higher in rural than in urban subdivisions in contrast to that for first dose reactors Among residents from Louisiana farms 72 per cent responded to the second dose and only 9 per cent to the first

Distributions representative of the southern part of the country could be viewed as distortions of the normal and must be explained either by reduced level of sensitivity among the infected or by local existence of nonspecific allergy among those not infected with tuberculosis Since the first explanation would necessitate acceptance of the extremely complex consequences of the assumption that tuberculous infection in certain parts of the country fails to sensitize to the usual degree the second appears much more acceptable Apparently the southern population is composed not only of those who have been infected with tuberculosis and noninfected persons but also of persons with nonspecific allergy The allergy may be caused by infection with an organism allergenically related to the tubercle bacillus The localization in Louisiana and Mississippi and the urban rural relation suggest that certain conditions such as climate soil and vegetation may be important factors influencing such nonspecific tuberculin sensitivity Person to person contact as in tuberculosis is probably not significant in this respect

[From time to time the question arises as to whether clo ely related or cross reactions may not be due in some cases to the presence of antigens of saprophytic mycobacteria This explanation was sugge ted for tuberculin reactions in cattle without dem nstrable tuberculous lesions Long (Am Rev Tuberc 63 355 359 March 1951) has c ted experimental evidence which suggests that saprophytes may occasionally be responsible —Ed]

Study of Chemical Mechanism of Tuberculous Caseation Characteristics of Fats of Caseous Material According to I Grundland H Bulliard and M Maillet[1] (Paris) lipids are

(1) P m d 59 406 407 M 8 1951

tients Old tuberculin and PPD prepared from M tuberculosis isolated from one of the patients caused tuberculin reactions in controls of the same intensity as those developing by simultaneous testing with ordinary OT Tuberculin neutralizing factor (anticutin) was found in the serum of one patient results for the factor were equivocal in a second and negative in two others This evidence does not provide convincing support for the idea that tuberculin neutralizing factor causes the negative tuberculin reactions in these cases

[The occurrence of bacteriologically proved and unhealed tuberculosis in tuberculin negative patients remains unexplained However such an occurrence is most exceptional and does not depreciate the value of the tuberculin test in differential diagnosis There are a number of nontuberculous lesions which resemble tuberculosis clinically and roentgenologically and there are unusual cases in which these lesions are associated with nonpathogenic saprophytic acid fast bacilli —Ed]

Studies of Pulmonary Findings and Antigen Sensitivity among Student Nurses Geographic Differences in Sensitivity to Tuberculin as Evidence of Nonspecific Allergy Carroll E Palmer Shirley H Ferebee (U S Pub Health Service) and O Strange Petersen[9] (Copenhagen) based their studies on tuberculin tests, using a first dose of 0 0001 mg and a second of 0 005 mg PPD S in 10 000 white student nurses in 10 widely separated metropolitan areas in the United States Only nurses who had spent at least five sixths of their lives in the same place were selected and all were tested within 12 months after admission to training

In the 29 states represented percentage of first dose reactors varied from 4 6 to 27 8 Low rates predominated for states in the north and west and high rates were found in the industrial centers of the east and in some southern states There was considerable irregularity in location of high and low prevalence areas of first dose reactors In general the frequency of first dose reactors conformed with other indexes of the prevalence of tuberculosis There was a substantial but not very high correlation between tuberculosis mortality rates for the white population in these states and the percentage of first dose reactors

Reactions to the second or high dose were strikingly independent of first dose reactions and showed a peculiar geographic pattern Throughout most of the country a remarkably constant proportion of approximately 24 per cent of all

(9) Pub Health R p 65 1111 1131 Sept. 1 1950

Effect of Organic Acids on Mammalian Tubercle Bacilli was studied by Rene J Dubos (Rockefeller Inst) Growth in vitro was inhibited by addition of sodium salts of certain organic acids in low concentration to a variety of liquid and agar culture mediums containing whole serum or serum albumin Capric acid was the most active compound tested but growth was also inhibited with the shorter aliphatic acids Lactic acid was inhibitory whereas keto and dicarboxylic acids were inactive in this respect Inhibitory activity was increased as the pH of the medium was lowered by addition of hydrochloric acid It was greater in mediums enriched with serum or oleic acid albumin complex The inhibitory effect appeared to be bacteriostatic rather than bactericidal and depended on a disturbance of the normal metabolic processes of the organisms

These findings may be of some significance with regard to survival and multiplication of tubercle bacilli in vivo within inflammatory and caseous areas Such areas are often acidic and contain high concentrations of organic acids Although there is lack of convincing quantitative data it may be assumed that the concentration of organic acids and the pH prevailing in inflammatory areas are similar to those used in the present study and exert a bacteriostatic effect on tubercle bacilli Despite results of the present study there is much evidence that the ability of the infected host to overcome infection ultimately depends on the power of its monocytes to kill the bacilli that they have engulfed

Interpretation of Results Obtained from Cultivation of Sputum Samples for Mycobacterium Tuberculosis Edgar M Medlar Sidney Bernstein and Fredric C Reeves[3] (Veterans Admin Hosp Sunmount N Y) made a comparative study of five mediums using 447 smear positive and 1 710 smear negative specimens (1) egg yolk potato medium (American Trudeau Society with slight modification) (2) oleic acid albumin agar medium of Dubos (3) Herrold s egg yolk agar medium (4) Jensen s modification of Lowenstein s medium and (5) modified Petragnanni s medium (difco®)

In each comparative study some of the smear positive

(2) J Expe M d 9 319 332 O t 1 1950
(3) Am J P b H lth 41 92 301 M h 1951

the chemicals of importance in tuberculosis constituting 22 7 30 per cent of the weight of the tubercle bacillus Some of the constituent fatty acids may cause a cellular reaction of a tubercular type in the peritoneum Some of the fat appears to absorb streptomycin and the effectiveness of the antibiotic is improved by adsorbing certain fatty acids (higher than C_{18} chains) on the surface of the organism Alkylstreptomycila mines have increased potency by virtue of their fat adherence The caseous material of the tubercle contains 13 77 23 79 per cent of fat (dry weight) of which 25 8 33 5 per cent is choles terol It is therefore unlikely that the caseous fats are de rived only from the tubercle bacillus lipids which do not in clude cholesterol Furthermore the caseous material is appar ently poor in bacilli These considerations led the authors to study the fats of caseous material and the reactions to mycolic acid from the tubercle bacillus Analysis of glycerides sterols and phosphatids were carried out to see if the distribution of fatty substances differed from those of protoplasmic fats Caseous nodes lung and kidney were fixed in various solu tions and stained for different fats

Giant cells were found to have a high fat content a small portion in the cytoplasm corresponded to phosphatids The sterols appeared as disseminated granules in the cytoplasm Glycerides were computed by deducting these fractions from the total fat Injections of mycolic acid caused formation of nodes with giant and epithelioid cells resembling those seen in tuberculosis The fats appeared early in the giant cells regrouping the protoplasmic fats around the lipids of the tubercle bacillus These lipids incapable of oxidative catabo lism have a greater affinity for protoplasmic fats than do proteins The chemical linkages involved can be analyzed by physical chemical means (dispersion forces of London)

[Knowledge of the complex chemical composition of the tuberculous lesion would probably go far in explaining the phenomena of necrosis coagulation and frequent failure of the necrotic mass to slough out as contrasted with rapid liquefaction in other lesions as well as later inhibi tion of bacterial growth and sometimes ultimate sterilization Some of these factors appear to be involved in nonspecific resistance to the infec tion Chemical research offers much promi e as indicated by this investiga tion and that which follows The possible affinity of some of the constitu ents of the tuberculous lesion for streptomycin is most interesting and may throw some light on the mechanism of action of this and other antimi crobial agents —Ed]

tinins were demonstrated in 80 per cent of 104 patients in whom diagnosis of tuberculosis was established by detection of tubercle bacilli and in 6 with typical symptoms and signs of tuberculosis in whom tubercle bacilli could not be demonstrated Serum from 26 of 28 healthy persons with negative tuberculin reactions and from 11 with various diseases and negative tuberculin reactions showed negative hemagglutinin titer Results were negative in 8 of 10 persons known to have had active tuberculosis which had been arrested for a long period

*In 50 per cent of 71 healthy persons with positive tuber*culin reactions there were positive hemagglutinin titers in contrast with the results in the normal persons with negative skin reactions who had no antibodies in their blood This suggests that antibodies had been stimulated by injection of *tuberculin since in most cases the tuberculin test* was performed before serum was collected for the hemagglutination test These findings were confirmed by results of hemagglutination *tests in normal subjects performed before and after* administration of tuberculin Among 13 persons in whom re*sponses to the hemagglutination and tuberculin tests* were negative 10 later showed positive hemagglutinin titers and 13 had positive tuberculin reactions seven weeks after administration of BCG

Of 11 patients with sarcoidosis 7 had positive hemag*glutinin titers*

[The hemagglutination test has received much study this and two following articles reflect some of the present interpretations and op n ons *Kirby and Burnell (Am J Med. 10 761 June 1951) do not consider the* test of much diagnostic value since they obtained false positive results in 10 per cent of patients w th nontuberculous di ease Fleming Runyon and Cummings (Am J Med 10 704-710 June, 1951) bel eve that an elevated titer favors tuberculo is in differential diagnosis although low or negat ve t ters do not rule out active tuberculosis In sarcoidosis t ters were m lar to tho e in normal adults in whom titers were occasionally high As Middlebrook suggests the test though not entirely pecific s of value in cl nical judgment hen weighed w th ther findings —Ed]

Practical Application of Hemagglutination Reaction in Tuberculosis Sidney Rothbard A S Dooneief and K E Hite[5] (Montefiore Hosp New York City) present data which confirm and extend the observations of Middlebrook and Dubos on the specific agglutination of sheep erythrocytes sensitized with antigen from tubercle bacilli by serums of

(5) P oc. Soc. E per B l & Med 74 2 5 M y 1950

concentrates were unproductive All mediums except no 3 appeared equally capable of stimulating growth of M tuberculosis With no 2 cultures had to be examined microscopically to identify growth in many instances before the fifth week The growth on no 1 was more luxuriant and more rapid than on other mediums in many instances and visual recognition was possible at an earlier date Similar conditions pertained to the cultures of smear negative specimens

In about 15 per cent of smear negative specimens possible detection of M tuberculosis was interfered with by overgrowth of secondary organisms Such interference was present in only 2 per cent of smear positive specimens Overgrowth with secondary organisms was as low on medium no 1 as on any other whereas the largest number of contaminations was found on no 2

There were 143 instances in which growth occurred on one medium only and in which neither medium was overgrown with secondary organisms Of these 116 were on medium no 1 and only 27 on all the other mediums Although there were at least twice as many cultures positive on no 1 only as on the other mediums the greatest difference between mediums was noted with no 2 and 3 both agar bases

The procedures used for growing M tuberculosis in a routine diagnostic service should be geared to the most efficient method for obtaining growth when bacilli are present in small numbers The results indicate that the slightly modified A T S medium is equal if not superior to others

[The point is to be stressed that some culture mediums while possessing pecial advantages in investigative work may not be as serviceable as others for utilitarian diagnostic purposes The desirability of a dependable technic in the laboratories of general and specialized hospitals is frequently impressed on one confronted with the problem of refined differential diagnosis The medium recommended here seems to be as serviceable and reliable as any recommended Frisch and Tarshis (Am J Med. 10 761 June 1951) describe a simple dehydrated agar medium with 25 per cent human bank blood which they consider suitable for sputum and pure cultures —Ed]

Clinical Interpretation of Middlebrook Dubos Hemagglutination Test After substituting a commercial tuberculin preparation for the special extract used by the original investigators David T Smith and Nancy B Scott[4] (Duke Univ) performed 800 tests on about 400 persons Hemagglu

(4) Am. Rev T berc 62 121 127 A g t 1950

glutination test for tuberculosis are noted (1) In skilled hands the high degree of specificity of the reaction suggests *that a positive reaction at 1 8 or higher dilution of serum is* presumptive evidence of disease due to tubercle bacilli or to a mycobacterium closely related in antigenic structure (2) *A certain percentage of persons with clinically active tubercu*lous disease fail to give a positive hemagglutination reaction either because of the severity of illness or because of inability *to produce antibody against the antigen involved in the test* (3) Results become negative after a period of freedom from spreading disease even when visable tubercle bacilli are still *present in the tissues* (4) Reactivation may be detected by the test before other evidence is obtained by present diagnostic methods (5) No conclusions regarding the patient s state of resistance are justified on the basis of test results The reaction titer is not a measure of the degree of activity of the disease (6) Undue stress on the hemagglutination test in contrast to a comprehensive clinical bacteriologic and x ray evaluation is poor medical practice

***Study of Adolescent Children Inoculated with BCG in* Early Infancy** Milton I Levine[7] (Cornell Univ) presents a follow up report on 601 persons aged 12 23 who had been vaccinated with BCG *in infancy* and 564 controls Chest x rays were obtained on 298 of the vaccinated and 286 controls Of the vaccinated patients three had x ray evidence of healed primary complex and two of reinfection tuberculosis Studies showed that the BCG vaccine was weak or inadequate in two of the first three and that in the third vaccination was carried out in the preallergic phase of a human tuberculosis infection In the two with reinfection tuberculosis the allergy after a weak BCG inoculation in one subsided and the child had a subsequent exposure to open tuberculosis with later development of reinfection tuberculosis The second showed evidence of *having lost the tuberculin allergy about three* years after inoculation

Among the 286 controls 27 had definite calcific deposits in the lung fields evidence of a healed primary complex There were no cases of reinfection tuberculosis in the control group

It is extremely difficult to determine the efficacy of BCG unless some method of maintaining the potency is devised and

(7) Pediatrics 6 853 861 December 1950

tuberculous patients The original test was slightly modified including use of old tuberculin concentrated four times its normal strength

Of serums from 110 normal adults 105 contained no antibodies and in the others they were present in low titer Of serums from 106 patients with nontuberculous diseases 98 gave negative reactions and 8 gave reactions in dilution of 1 2 Of 168 patients with active bacteriologically proved tuberculosis serums of 155 gave positive reactions in titers of 1 8 1 512 Serums from some patients with minimal moderately or far advanced pulmonary tuberculosis gave negative reactions Among 33 persons who had been in good health at least seven years but at one time had had active pulmonary tuberculosis the serums of 2 reacted in 1 2 dilution the rest showed no reactions

In 10 of 120 tuberculous patients whose serums were tested at monthly intervals antibodies were no longer detectable by this technic Their disappearance was correlated with absence of disease activity and failure to demonstrate tubercle bacilli in the sputum or gastric contents on smear or culture

The hemagglutination test apparently is a valuable diagnostic tool but its greatest value may lie in demonstrating the presence of tuberculous activity

Hemagglutination Test in Tuberculosis In 1948 a highly specific hemagglutination reaction was described which readily revealed antibodies in the serums of patients with active tuberculosis Addition of complement to the hemagglutination system transforms the reaction from specific agglutination of red cells to hemolysis this hemolytic modification seems to have advantages over the original agglutination test

The material which sensitizes red cells in the hemagglutination reaction appears in culture filtrates of tubercle bacilli only in association with lysis of the organisms Gardner Middlebrook[6] (Rockefeller Inst) postulates that release of antigens which stimulate production of the antibodies responsible for the hemagglutination reaction ceases soon after the bacilli stop multiplying and spreading There is no evidence that the antibodies measured in the test are directly related to the mechanism of protection

The following possible limits of usefulness of the hemag

(6) Am Re T berc 6 2 3 26 A g t 1950

but also in general ho pitals the fear which has developed among pro fessional workers is not fully ju tified by the known facts This fear adds *to the difficulties of nursing tuberculous patients The problem of infection* is complicated by the compensability as an occupational disease in many *states Canetti and Robert (Rev tuberc 14 451 457 1950) found a higher* incidence of relapses among physicians who recovered from tuberculosis *and remained to work in tuberculosis ho pitals than among those return* ing to private practice and they interpreted this in favor of exogenous *superinfection The validity of this conclusion may be questioned in view* of other factors which would play a part Dahl (Acta tuberc scandinav *24 75 79 1950) attacks the study of Heimbeck purporting a threefold* mortality from tuberculosis among heavily exposed nursing probationers *compared to Oslo women of the same age Considering false positive* tuberculin tests the greater manifestation of disease during the first year *after primary infection the possib lity of better selection in towns and* better observation of the probationers Dahl believes the morbidity to be *the same in the two groups Autopsy evidence seems to indicate only oc* casional superinfection so long as pre existing lesions are not completely healed —Ed]

Study of Relation of Nutritional Status to Pulmonary Tuberculosis Charles R Shaw Frederick Beck Helen Pilcher and June Parker[9] (Cornell Univ) determined the serum con tents of hemoglobin vitamins A and C carotene alkaline phosphatase and total protein in 187 adults with pulmonary tuberculosis and 118 nontuberculous adults Dietary studies were made on 25 tuberculous patients and 17 controls

Intake for most nutrients was qualitatively similar for the groups It was about 50 per cent higher for the controls probably because of their greater physical activities most of *them being rural workers There was little or no correlation* between the status or stage of tuberculosis and the blood levels of the factors studied A possible exception was the hemoglobin level which was lower in far advanced cases than in controls There was a close correlation between symptoms and the blood concentrations of all nutrients studied No sin gle nutrient appeared more affected than others but there was a general trend downward in the blood concentration of all nutrients as the symptoms became more severe

[Such careful studies empha ize the impairment of nutrition by tuber culo is There is great need for more studies concerning the nutritional factors which seem to favor development of the d sease —Ed]

Experimental Tuberculosis Effects of Anastomosis be tween Systemic and Pulmonary Arteries on Tuberculosis in Monkeys C Rollins Hanlon and H William Scott Jr (Bal timore) and Byron J Olson[1] (Bethesda Md) altered pul

(9) Am. R T be 62 58 64 J ly 1950
(1) S g y 8 209 2 4 A gu t 1950

a standard accurate means of inoculation (preferably the intradermal method) used If the tuberculin reaction is not positive two months after vaccination, the procedure should be repeated Revaccination should be carried out subsequently whenever the skin reaction again becomes negative

[The question of the exact merits of BCG remains rather controversial Its harmlessness is assumed from vast clinical experience although under highly artificial conditions progressive and fatal pulmonary disease can be produced by BCG organisms This was accomplished by Vorwald Dworski Pratt and Delahant (Am Rev Tuberc 62 455 474 November 1950) in guinea pigs having silicosis from inhalation of quartz dust BCG did not protect these animals from tuberculous infection produced by attenuated R_1 organisms On the other hand Poulain (Rev tuberc 14 495 500 1950) is conducting a study of protection conferred by BCG against tuberculosis among young workers in the Saare and Moselle mines Most workers agree that immunity evoked by BCG is only partial and relative and is probably less reliable and of shorter duration than that conferred by natural infection The advantage of course is the relatively low virulence of BCG Thus it is still widely favored as a means of partial protection of people living in highly contaminated areas —Ed]

Tuberculosis in Student Nurses and Medical Students at University of Wisconsin was reviewed by Helen A Dickie[8] Tuberculosis developed in 19 of 188 originally tuberculin negative medical students in the classes of 1934-43 but in only 2 of the original 95 tuberculin reactors In the classes of 1944 47 tuberculosis developed in 6 of 44 original tuberculin negative students and in 2 of 46 original tuberculin reactors Of the 106 who received BCG vaccination 1 has tuberculosis

Experiences in student nurses during the same periods were similar Three student nurses had x ray evidence of tuberculosis at the time of the first positive tuberculin test and in five it was detected on x rays within three to nine months after tuberculin conversion Among tuberculin converters in medical students there was 1 death 18 received sanatorium care and 7 with small lesions continued their work with limited activity On x rays the most common location of the parenchymal lesions was in the upper lung field especially in the infraclavicular area

Although environmental control of tuberculous infection must receive close attention because of continued exposures infection will occur in these professional groups despite the most rigid program Therefore BCG vaccination merits trial

[Though some extra hazard of infection exists not only in tuberculosis

(8) A n I t M d 33 941 959 Octobe 1950

sone Survival time reached 100 per cent for animals receiving tubercle bacilli alone 87 per cent for cortisone alone and 20 per cent for tubercle bacilli plus cortisone

Autopsy showed diffuse small pearly nodules in the lungs of rats infected with tubercle bacilli Microscopically the picture was that of an orderly well contained granulomatous process Animals given tubercle bacilli and cortisone had large caseous masses which sometimes involved whole lungs Microscopically these lesions showed diffuse interstitial pneumonitis with profuse alveolar exudation containing large numbers of mononuclear cells There was no attempt at tubercle formation

Cortisone enables tubercle bacilli in the rat to multiply more rapidly produce more diffuse lesions disseminate and result in death of the animal It seems to lower the host s natural resistance Caution should be used in administering cortisone to persons with active tuberculosis

[Other experimental investigators report rather similar alterations and aggravations of tuberculous lesions in various animals This subject was discussed in a symposium at the American Trudeau Society meeting in Cincinnati in May 1951 Cortisone has also been shown to suppress some early inflammatory reactions to the tubercle bacillus LeMaistre and associates (J Clin Invest 30 445 456 May 1951) reported a clinical study with ACTH and cortisone The immediate improvement of symptoms and lesions in some patients was striking though temporary In view of the experimental evidence it is suspected that aggravations of tuberculosis have followed use of these hormones for arthritis or other conditions and this result might be anticipated unless the tuberculous lesions are known to be well healed —Ed]

Results of Treatment of Active Minimal Pulmonary Tuberculosis with Modified' Bed Rest Statistical Analysis of 289 Patients Followed for Seven Years after Discharge from Trudeau Sanatorium was made by Roger S Mitchell and Jack R Knudson[3] The cumulative reactivation rate for 289 patients was 37 per cent In 60 per cent the phenomenon had appeared by the end of the first year after discharge but in nine patients the first reactivation occurred more than seven years after discharge Of the entire series 7 18 years after discharge only 3 per cent had died of tuberculosis and 4 per cent were chronically ill with the disease Except for those dead of nontuberculous causes the others were well and working when last contacted

Prognosis improved with passing years in females but

monary circulation by anastomosis between systemic and pulmonary arteries in monkeys infected intravenously with human tubercle bacilli Nine monkeys with end to end anastomosis lived 80 257 days after inoculation In eight the extent of pulmonary disease at autopsy was greater in the lung on the side of anastomosis Numerous conglomerate tuberculous lesions in this lung showed massive caseous areas in contrast to smaller less widely distributed tubercles in the opposite lung Lesions in the lung on the nonsurgical side were similar to those found in both lungs of control animals

Three monkeys with end to side anastomosis lived 79 81 and 262 days At autopsy the distribution of caseous lesions was equal in the two lungs in one animal but the disease process was much greater on the side of anastomosis in the other two

The 24 control monkeys died of widespread tuberculosis 76 186 days after infection Characteristically the tubercles were of miliary type and small Extrapulmonary lesions were similar in character and distribution to those in monkeys with arterial shunt

Diversion of systemic blood into the pulmonary arteries produces a pathologic process differing from the disease in control animals but the factors responsible for the differences are not immediately apparent In the lung on the side of the arterial shunt there are an increase in blood flow and oxygen content of the blood as well as alteration in the pulmonary arterial pressure There may also be changes in the usual hematogenous dissemination of tubercle bacilli The importance of each of these factors remains to be evaluated

[This is somewhat reminiscent of a treatment of bone and joint tuberculosis known as Bier s hyperemia treatment, in which tourniquets were applied to the limbs to produce congestion and hyperemia about the lesions In ome ca es this tr atment seemed to be beneficial but in others active lesions were reported to be aggravated Circulatory factors certainly seem to be important and they merit study —Ed]

Course of Experimental Tuberculosis in Albino Rat as Influenced by Cortisone Max Michael Jr Martin M Cummings and Walter L Bloom (Emory Univ) injected 2 mg of a young culture of Mycobacterium tuberculosis intraperitoneally into healthy rats Some of the animals were used as controls while the others were given 5 mg cortisone daily for 42 52 days Another group received only injections of corti

(2) Proc. Soc. Exper B L & Med. 75 613 616 November 1950

tuberculoma is a tumor like granuloma caused by the tubercle bacillus encapsulated by connective tissue and showing no evidence of surrounding inflammation or spread A pulmo

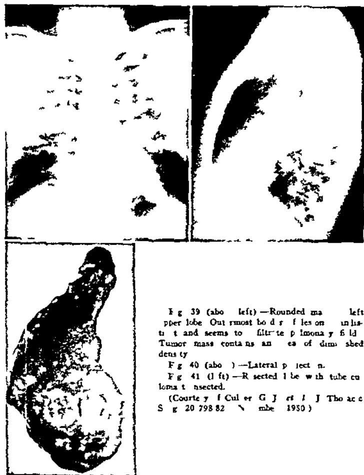


Fig 39 (abo left) —Rounded ma left pper lobe Out rmost bo d r f les on in his- ti t and seems to filtr te p lmona y fi ld Tumor mass conta ns an ea of dim shed dens ty

Fig 40 (abo) —Lateral p ject n.

Fig 41 (l ft) —R sected l be w th tube cu loma t nsected.

(Courte y f Cul er G J et l J Tho ac c S g 20 798 82 N mbe 1950)

nary tuberculoma may arise from (1) encapsulation of a giant primary focus—this focus may appear at any age (2) encapsulation of a restricted reinfection focus of tuberculosis that has a tendency toward rapid regression and becomes

age alone brought no significant differences. Results in males were not notably better than in females. There were no Negro patients in this series. Presumably recent lesions followed a more unstable course than the definitely old lesion. There was direct correlation between results and the average extent of pulmonary involvement on the flat chest film. Location of the disease had no bearing on late results. Lesions unchanged on serial x-rays during sanatorium residence presented significantly more favorable prognosis than those with slight or questionable increase of infiltration. There was also more favorable prognosis of probable significance when lesions with any degree of clearing were compared with the latter group. Rapidity and degree of clearing during sanatorium residence had no special bearing on results. Absence of symptoms before admission was a favorable prognostic sign. Results were not related to the finding of positive sputum at some time during residence. Sputum was positive in 64 per cent of cases. There was no significant difference in the mean duration of modified bed rest between persons having later reactivation and those who remained well for the next seven years.

Controlled and comparative studies are needed to assess the relative merits of modified bed rest, more lenient regimens and strict rest regimens in treatment of minimal pulmonary tuberculosis.

[Relapsing "minimal" tuberculosis should usually be considered a sign of chronicity, at least in the pathologic sense. Chronicity may have been established before the patient began rest treatment. Under such circumstances rest treatment is not as effective as it is in recently developed minimal lesions. It would be desirable, of course, to apply treatment to avoid the high percentage of relapses and chronicity reported in this study from one of our best institutions. "Modified" bed rest is a very relative factor depending on medical concepts and practices and on the individual reaction and co-operation of patients; the earlier the lesion and the less its necrosis, the more prompt and lasting will be the response. In some cases antimicrobial therapy may be added, but as yet it is not favored uniformly, chiefly because of the development of drug resistance. In young persons, more chronic minimal lesions which give rise to persistent or recurrent positive bacterial cultures and act as source of occasional small increases or spreads of the disease are being removed surgically in well selected cases, usually with success.—Ed.]

Pulmonary Tuberculomas: Pathogenesis, Diagnosis and Management. According to Gordon J. Culver, Joseph P. Concannon and Joseph E. MacManus[4] (Buffalo Gen'l Hosp.) a

(4) J. Thoracic Surg. [illegible], November, 19[illegible].

calcified mass in serial x rays over a few months is not evidence that the mass is benign A peripheral lesion without a definite diagnosis demands operative exploration

[Many tuberculomas (a generally us d but not very appropriate term) are poorly f at all encapsulated with fibrous ti ue In young persons particularly they are l kely to be more or le in pissated or liquefied ca eous abscesses which may slough out leading to bronchial dis emination of infection D pending on the history age of the patient and duration of the lesion some of these lesions should be re ected after a well conceived cour e sometimes prolonged of antibiotic therapy to clear up as much as po ible of the peripheral non necrotic exudate There is a growing tendency to remove surgically solitary pher cal or circum cribed pulmonary le ions without delay becau e of the pos ib lity cf cancer However the nature of many of these lesions can be determined or trong ly inferred by thorough study and there is a reasonable medium between precipitate surgery and unseemly delay for observation—Ed]

Controlled Investigation of Streptomycin Treatment in Pulmonary Tuberculosis Esmond R Long and Shirley H Ferebee (Nat l Inst of Health) report results of 12 months observation on 271 control tuberculous patients and 270 who had streptomycin in addition to the usual therapeutic measures The two groups were comparable in age sex color type and extent of disease in 44 streptomycin and 77 control cases the study was incomplete The experimental group received streptomycin (20 mg/kg body weight) for 91 days a second course was given to 27

During the 12 months 21 of the streptomycin group and 40 controls died In both groups the mortality rate was higher for males than for females and among nonwhites than among whites

Underweight patients who received streptomycin showed a greater tendency to gain weight than did controls The number of febrile patients in the streptomycin group dropped sharply at three months and remained at about 5 per cent throughout the year The decrease was much slower in the control group but at the end of 12 months there were fewer with temperatures above 99 6 F than in the streptomycin group At the end of three months in the streptomycin group the proportion of patients producing virtually no sputum had definitely increased and it continued to do so more slowly throughout the year In the control group there was a much slighter and more gradual increase in the proportion without sputum and a tendency to move into the dead category

(5) P b H lth R p 65 14 1 1451 N 3 1950

homogeneous (3) a completely blocked tuberculous cavity with resultant inspissation of caseous material fibrosis cal cification and shrinkage of the occluded cavity (this cavity may occur in the reinfection focus and rarely in the Ghon focus)

X ray diagnosis of circumscribed solitary shadows in lung fields is often difficult x rays cannot always be relied on for adequate differentiation Differential diagnosis must always include primary and secondary neoplasms tuberculomas en capsulated effusions cysts abscesses, localized areas of pneu monitis hamartoma of the lung arteriovenous aneurysms and other rarer lesions The solitary circumscribed shadow of the tuberculoma is easily confused with peripheral pulmonary carcinoma (Figs 39 and 40) So far as is known x rays have never shown calcification in primary malignant tumors but have shown it occasionally in tuberculomas Most solitary peripheral masses with or without surrounding infiltration will prove to be carcinoma This peripheral type constitutes about 25 per cent of all primary lung tumors Figure 41 shows a transected tuberculoma in a resected lobe

The problem of deciding the best treatment for a patient with an asymptomatic solitary well circumscribed mass in the lung field requires the use of every available diagnostic method The patient should be fluoroscoped and x rays taken Primary neoplastic disease of other organs should be ruled out Bronchoscopy should be carried out and biopsy done if possible Secretions obtained bronchoscopically and sputum should be examined for cancer cells and tubercle bacilli The tuberculin test should always be done Biopsy of enlarged peripheral nodes is indicated Intrapleural fluid should be as pirated and cytologic and culture studies performed Tomog raphy may be of value in demonstrating calcification

Immediate surgery is recommended for the solitary round tumor without calcification with or without areas of cen tral breakdown If the mass is peripheral it may be readily examined at operation and local resection performed if it is non neoplastic Mo t lesions located at the hilum are malig nant there is no alternative but exploration and pneumonec tomy if advisable Well calcified tuberculomas without areas of breakdown can probably be considered stable and surgery is not usually desirable The unchanged appearance of a non

Para aminosalicylic acid has been satisfactorily administered subcutaneously and intravenously by a number of clinicians when patients could *not tolerate the drug by mouth because of gastrointestinal disturbances* A purified (lyophilized) sodium salt is used for this purpose —Ed.]

Treatment of Pulmonary Tuberculosis with Streptomycin and Para Aminosalicylic Acid Medical Research Council Investigation is reported by Marc Daniels[6] Of 166 *patients with acute progressive bilateral pulmonary tuberculosis* 59 were treated with PAS 20 Gm as sodium salt daily 54 with streptomycin 1 Gm daily and 53 with streptomycin and PAS Therapy was given for three months and observation continued for an additional three months

PAS alone was less effective than streptomycin alone Although the x ray condition deteriorated in only a few patients *given PAS 34 per cent showed no appreciable x ray* change during observation compared with 6 per cent of those receiving streptomycin Less than a fourth of patients given PAS but more than half those given streptomycin showed x ray improvement of considerable degree The difference was noted particularly in febrile patients Fewer PAS treated cases became bacteriologically negative and the differences *in clinical improvement were also less obvious*

When the two groups receiving streptomycin were compared the outstanding difference was in the emergence of streptomycin resistant strains of tubercle bacilli Such resistance was detected in 33 patients given streptomycin and in 5 given both drugs Most of the therapeutic differences between the two groups were not great and did not satisfy tests of statistical *significance Improvement was somewhat greater* in the patients who received PAS and streptomycin than in those who received streptomycin alone On x rays 87 per cent of the former and 74 per cent of the latter showed improvement Sedimentation rate was normal at six months in 40 per cent of the combined treatment group and 21 per cent of the streptomycin group The clearest effect of combined treatment apart from that of drug resistance was on the bacterial content of the sputum In the sixth month tests in 33 per cent of the combined treatment group and 19 per cent of the streptomycin group were bacteriologically negative

Although the course of disease was less favorable in patients with *resistant strains and clinical relapses were more*

(6) B M J 2 1073 1085 N 11 1950

rather than into the improved ratings In both groups tubercle bacilli were found in nearly 100 per cent at the beginning of the study and in only about 50 per cent at the end of a year Decrease was more rapid among those receiving streptomycin. In about 70 per cent of the streptomycin group chest x rays showed improvement at the end of three months which con tinued during the next nine months The number showing no change during streptomycin therapy decreased from 16 per cent at 3 months to about 7 per cent at 12 months The proportion showing deterioration increased slowly as the no change group decreased Among controls changes in chest x rays were much slower and less dramatic

Although at the end of three months the streptomycin group showed strikingly superior improvement differences between the two groups decreased somewhat as length of time after streptomycin therapy increased

[Demonstration of the efficacy of streptomycin against tuberculosis and of the similar though less pronounced action of para aminosalicylic acid has led to much comparison of the two drugs and particularly to observations of their effects when given in combination The high incidence of bacterial resistance against streptomycin after courses of three to four months places a limit on the use of this drug alone Dye and Gogley (U S Armed Forces M J 1 1137 1140 October 1950) and others have demon strated similar resistance to para aminosalicylic acid in a smaller but still considerable proportion (19 of 37) of patients treated 120 days or longer Both drugs have potential toxic properties which now can be anticipated and guarded against by regulating dosage and schedule of administration

The following two studies indicate that a great advantage of combined administration seems to be the postponing of manifestations of bacterial resistance and the prolonging of therapeutic effects Tempel and associ ates reduced the streptomycin administration to an intermittent schedule. At the Tenth Conference on Chemotherapy of Tuberculosis Veterans Ad ministration held in Atlanta in January 1951 D Esopo and co-workers reported on the prolonged use of combined therapy with continuing bene fits after a year or more in some cases Within this time the discharge of tubercle bacilli from open tuberculous cavities may be suppressed com pletely at least temporarily In some cases surgical treatment became permissible for the first time Other antimicrobial drugs o far tested when used with streptomycin do not seem to have the same advantages

Studies on dihydrostreptomycin continue because compared with streptomycin it has less toxic effects on the vestibular apparatus How ever dihydro treptomycin has been reported to cause more frequent dam age to the auditory nerve sometimes with deafne s which may continue and increase after treatment Such a report is that of O Connor Christie and Howlett (Am Rev Tuberc 63 312 324 March 1951) This damage eems more common after use of the hydrochloride salt and is thought to be due to some impurity dihydrostreptomycin sulphate may possibly be less toxic Current studies are expected to provide more information

most x ray improvement was only slight Sputum conversion occurred in 15 per cent receiving streptomycin daily 8 per cent receiving PAS daily 21 6 per cent receiving streptomycin every three days and 37 per cent on combined therapy Before treatment all organisms cultured were sensitive to streptomycin and PAS but after treatment sensitivity persisted only in the group receiving combined therapy Patients treated with streptomycin daily showed the greatest incidence (57 5 per cent) of toxic reactions

Evaluation 60 days after treatment showed clinical relapse of 15 1 22 2 per cent X ray worsening varied from none in the PAS group to 14 8 per cent in the streptomycin daily group Bacteriologic relapse ranged from 5 5 per cent in the PAS series to 31 2 per cent in the streptomycin PAS series Some degree of post treatment relapse was expected since cavities persisted in about 50 per cent of all patients whose sputum became negative during treatment The fact that collapse procedures or excisional surgery were required (36 4 per cent of the streptomycin daily group to 75 2 per cent in those given streptomycin intermittently) indicates that drug therapy is rarely definitive for nonmiliary pulmonary tuberculosis On the other hand drug therapy enables more patients to undergo various collapse procedures or excisional surgery at an earlier date with less danger of complications Streptomycin every third day combined with PAS daily is the regimen of choice for periods up to four months

Benemid and Carinamide Comparison of Effect on Para Aminosalicylic (PAS) Plasma Concentrations William P Boger Forrest W Pitts and Martin E Gallagher[8] (Philadelphia Gen l Hosp) state that the average result from six patients who received carinamide or benemid on separate occasions strikingly demonstrates the equality of the effects of these two agents on the plasma concentrations of PAS With either agent there was no significant difference in the plasma concentrations of PAS observed one half and two hours after administration of a single dose of 4 Gm NaPAS The time required for distribution of PAS in the body fluids appears to be the most reasonable explanation of this finding At four six and eight hours two to fourfold increases of PAS plasma concentrations were observed with both drugs

(8) J Lab & Cl M 36 276 82 Aug 1950

apt to occur in such cases many patients with resistant strains continued to show improvement indicating that drug resistance must not be overstressed in prognosis PAS given alone has a place in treatment of patients showing apparently complete streptomycin resistance The combination of PAS with streptomycin not only renders administration of streptomycin effective for longer periods than previously but probably permits repeated effective courses In using chemotherapy when healing might be expected without either collapse treatment or chemotherapy, it should be remembered that neither PAS nor streptomycin is without toxicity and that the emergence of streptomycin resistance is not entirely prevented by combined therapy

Combined Intermittent Regimens Employing Streptomycin and Para Aminosalicylic Acid in Treatment of Pulmonary Tuberculosis Comparison with Daily and Intermittent Dosage Schedules Carl W Tempel Frederic J Hughes Jr Richard E Mardis Milton N Towbin and William E Dye[7] (Fitzsimons Army Hosp) treated 66 patients with streptomycin 1 or 2 Gm daily 25 patients with para aminosalicylic acid 12 Gm daily 97 patients with streptomycin intermittently 1 or 2 Gm every third day and 95 patients with a combined regimen of streptomycin 1 or 2 Gm every third day and para aminosalicylic acid 12 Gm daily Treatment was continued for 120 days All patients had moderately or far advanced nonmiliary pulmonary tuberculosis with tubercle bacilli demonstrated at beginning of therapy none had received previous chemotherapy Operative procedures were deferred until completion of drug therapy Cavitation was present in about 90 per cent of each group Incidence of tuberculous complications varied from 8 to 27 per cent

Evaluation after completion of therapy showed improvement of clinical status ranging from 56 per cent of patients on PAS to 72 8 per cent of those on streptomycin daily Clinical status deteriorated in 8 per cent of those who received PAS daily to 29 8 per cent of those who were given streptomycin every three days X ray improvement was noted in 88 5 per cent of those on combined therapy 71 4 per cent receiving streptomycin every three days 76 per cent receiving PAS daily and 74 per cent receiving streptomycin daily In

( ) Am Rev T berc. 63 295 311 March 1951

Tuberculostatic Action of Terramycin in Vitro and *in the* Experimental Animal W Steenken Jr and E Wolinsky[1] (Trudeau Found) found that 5 10 μg terramycin/cc liquid medium was sufficient to inhibit growth of H37 Rv strain of tubercle bacilli in both tween® albumin and Proskauer and Beck s plain synthetic medium The streptomycin resistant strain was as sensitive to terramycin as the streptomycin sensitive strain No increase in resistance to terramycin was exhibited after five transfers in tween® albumin medium containing the drug

Subcutaneous injections of 0 13 mg streptomycin sensitive micro organisms were made into 73 tuberculin negative guinea pigs and similar amounts of streptomycin resistant organisms were injected into an additional 38 animals The animals were then divided into groups and treated with various antibiotics Terramycin and viomycin greatly retarded growth of tuberculous infection in guinea pigs given either streptomycin sensitive or resistant tubercle bacilli Both these agents when administered in maximal tolerated doses were more effective than para aminosalicylic acid tibione® aureomycin and *NF(5 nitrofurfural thiosemicarbazone)* Terramycin proved highly toxic daily doses as low as 2 5 mg producing weight loss and bloating of the abdomen Other experiments indicated that terramycin had definite antituberculous activity in mice with experimental murine tuberculosis

[Terramycin may have some effect in human tuberculosis although its effect is sometimes questionable and is certainly not as great as that of streptomycin Terramycin has been taken by some tuberculous patients in doses of 5 Gm or more daily for many days without untoward effects others cannot tolerate even small doses

Other more or less familiar antimicrobial agents include the thiosemicarbazones (tibione® etc) In doses of 200 300 mg daily they have caused blood dyscrasias and toxic effects on the liver Doses of 50-100 mg daily seem less toxic but there is generally much skepticism about the therapeutic effects of tolerated doses

Promizole® is still being used over many months or several years for generalized miliary tuberculosis in the Children s Chest Service of Bellevue Hospital Nemir Schulman and Clemons (Am Rev Tuberc 62 618 631 December 1950) emphasize the necessity of controlling the dosage (0.5 1 Gm daily guided by age in divided doses every six hours) to give a blood concentration of 1 2 mg /100 cc The drug has a goitrogenic effect but no other significant toxicity

Neomycin while active against streptomycin resistant strains of the tubercle bacillus has been disappointing clinically because of the great

(1) Am Rev Tuberc 62 309 318 Sept 15 1950

The striking fact is that these levels were maintained by administration of 0 5 Gm benemid every six hours whereas for similar results 3 Gm carinamide every three hours was required The small daily dosage the fact that it can be administered at widely spaced intervals and the nontoxicity of benemid make it probable that the agent will have a practical application in enhancement of therapeutic effectiveness of PAS in tuberculosis

[Use of this drug with para aminosalicylic acid may have the merit of permitting a lower dosage of para aminosalicylic acid while maintaining a satisfactory blood level —Ed]

Viomycin in Tuberculosis of Guinea Pigs Due to Streptomycin Sensitive and to Streptomycin Resistant Tubercle Bacilli was investigated by Alfred G Karlson and Joseph H Gainer[9]

METHOD —Thirty six guinea pigs were infected with a streptomycin sensitive strain of tubercle bacillus and 36 with a streptomycin resistant strain After 24 days six animals from each group were killed (they had grossly visible lesions in the usual organs) The rest of the animals in each experiment were divided into three group of 10 animals each One group served a untreated controls in one animals were treated with 6 mg streptomycin once daily in one animals were treated with 20 mg viomycin once daily Treatment was started on the 24th day of infection and continued for 61 days after which all surviving animals were killed

In animals infected with streptomycin sensitive organisms results of viomycin therapy were comparable to those produced by streptomycin Treated animals had an impressive lack of visible lesions in the lungs liver and spleen In striking contrast all control animals had widespread tuberculous disease

Results in animals infected with streptomycin resistant tubercle bacilli clearly demonstrated the beneficial effect of viomycin since they were comparable to those achieved in infections due to streptomycin sensitive bacilli Administration of streptomycin to animals infected with streptomycin resistant bacilli had no beneficial effect

[Viomycin has definite therapeutic effects on tuberculosis in man but on the average does not appear to equal streptomycin Renal irritation or damage is common and the seriousness of this result has not yet been determined There is some disturbance of electrolytes with hypokalemia Viomycin also has neurotoxicity apparently similar to that of streptomycin Its possible place in therapy is still being investigated —Ed]

(9) Proc Staff Meet Mayo Cl 26 53 59 Ja 31 1951

have been previously treated with the drug This may be interpreted in ferentially to indicate the intre juency of exogenous sup rinfection

The method of assessing treptomycin resi tance described by the authors is interesting Otl ers have used a liquid medium which does not reveal the proportion of re i tant str ins in a bacterial populat on A plate method has al o been develope l which seems satisfactory Benda and Urquia (I ev tuberc 14 343 347 1950) report a microscopic method which they believe di tinguishes sensitive and resistant strains by their staining characteristics Resistant bacilli are said to stain homog neously losing the chromophilic granulations visible in the bodies of ensitive bacilli —Ed]

Pathogenesis of Certain Forms of Extrapulmonary Tuberculosis Spontaneous Cold Abscesses of Chest Wall and Pott's Disease According to Hugh E Burke[3] (Montreal) experimental anatomic and clinical observations demonstrate that spontaneous cold ab cesses of the chest wall are lymph borne *sequelae of tuberculous pleuritis and that Pott s di ease is the* result of lymph borne dissemination of tubercle bacilli

When colloidal thorium dioxide finely divided lamp black or tubercle bacilli are introduced into the pleural spaces of guinea pigs some of this particulate matter is regularly transported to the parasternal and para aortic lymph nodes Tubercle bacilli introduced into the pleural spaces of vaccinated guinea pigs commonly evoke pleural effusions and frequently give rise to tuberculous lesions in the parasternal and para aortic lymph nodes Autopsy studies reveal that the lymph drainage system of the pleural spaces of man is comparable to that of the guinea pig

Experimental anatomic and in 14 cases clinical evidence corroborated the following concept of the evolution of mo t cold abscesses of the chest wall Tubercle bacilli invade the pleural space and set up local or widespread pleuritis Some bacilli are transported from the pleural space to the para sternal lymph nodes which become ca eous and rupture Necrotic and caseous material burrows anteriorly to form a cold abscess in the chest wall

In most cases of Pott s disease tubercle bacilli invade the pleural space and set up local or widespread pleuritis Some organisms are transported from the pleural space to the para aortic lymph nodes where tuberculous lesions develop Some of these lymph node lesions undergo necrosis and ca eation resulting in tuberculous abscesses The abscesses spread to the vertebral column and adnexa either by contiguity or by

(3) Am R T be 6 48 67 J ly 1950

frequency of deafness following its administration It is therefore contraindicated —Ed]

Primary Streptomycin Resistant Tuberculosis in New born Child Simple Method of Assessing Streptomycin Resistance J E Tinne and J L Henderson (Univ of Edinburgh) found miliary tuberculosis in an infant aged 11 weeks which yielded cultures of Mycobacterium tuberculosis with a high degree of primary resistance to streptomycin Source of the infection was the mother but neither she nor the baby had received streptomycin

A simple vertical diffusion test is described which shows higher degrees of streptomycin resistance than the standard Dubos test and indicates the number of resistant variants present This test is of value because prognostic information may be obtained before streptomycin therapy is instituted

METHOD—Into 1 oz screw cap vials 6 ml amounts of Lowenstein Jensen medium are poured and allowed to solidify as slopes in the usual manner After condensation water is decanted 1 ml streptomycin solution in strengths of 1 10 and 100 μg /ml is added at the base of each slope The vials are then labeled and kept refrigerated until required For the test after the specimen is concentrated standard loopfuls are inoculated by stroking the entire slope of plain Lowenstein Jensen medium and streptomycin containing mediums Use of the 1 and 10 μg /ml concentrations is essential in all cases the 100 μg /ml concentration is used in all cases showing increase in resistance during the course of treatment Similar cultures of the strain H37 Rv are made as controls Bottles are incubated in the upright position for three or four weeks at 37 C

Confluent growths are seen on the control slopes whereas those containing streptomycin show zones of complete inhibition extending from the foot of the bottle and varying in extent with the dose of streptomycin and sensitivity of the organism

If a patient has already been given streptomycin culture is often unsuccessful unless the organism is first grown on Lowenstein Jensen slopes which contain 2 mg cysteine hydrochloride/ml medium When growth has been obtained on this medium the organism is transferred to streptomycin containing medium for evaluation of its sensitivity

[The occasional reports of primary infections with streptomycin resistant bacilli from contact with patients treated with streptomycin have been anticipated since resistant strains do not lose virulence However it is rare thus far to find patients with long standing chronic tuberculosis who discharge streptomycin resistant strains of the bacillus unless they

( ) Lancet 901 904 Dec. 30 1950

Hematogenous dissemination was the commoner route by which the pleura was infected (46 times) seeding usually be ing from skeletal or urogenital sources In 15 instances the caseous pleural tuberculosis was the oldest active process aside from the healed primary complex

Of the 29 patients with tuberculous pericarditis 15 were Negroes Skeletal or urogenital tuberculosis was present in 15 cases Direct extension was noted in 8 hematogenous in fection usually from a urogenital or skeletal source in 13 and a healed primary complex in 8

Gross and microscopic appearances of tuberculosis of serosal surfaces were either those of caseous tuberculosis or those of *generalized miliary tuberculosis* *When the involve* ment occurred by direct extension from caseation within an organ caseous tuberculosis developed in the serosal cavity *Less often caseous tuberculosis developed after hematoge* nous dissemination Not all cases of hematogenous dissemina tion were characterized by miliary tubercles for in some in stances especially in the pleural cavity the foci were large and had caseous centers Healing occurred with scar tissue formation and obliteration of the space Sometimes areas of caseation became encapsulated by scar tissue and calcified Healing of serosal tuberculosis is most likely to occur if the underlying tuberculosis also heals

[This study points up the clinician s obligation to develop some con cept of the pathogene is in individual cases Serosal tuberculosis due to hemic dissemination of infection re ponds to treatment as the generalized disease improves but if the sero a is infected from lesions in adjacent structures such as bone or fallopian tube local persi tence and recurrence of disease may be anticipated until the underlying focus is dealt with effectively —Ed]

MYCOSES

Further Observations on Histoplasmosis Mycology and Bacteriology Michael L Furcolow[5] (Univ of Kansas) re ports 6 *new cases in which Histoplasma capsulatum was re* covered and adds material from 10 previously reported from the Kansas City area of the new patients 2 had recovered 1 was *still ill* and 3 were dead *None of the new patients had* skin reaction to blastomycin and four did not react to coccidi

(5) P b Health R p 65 965 994 A g 4 1950

way of communicating lymph channels In many instances Pott s disease is an end result Experimental and anatomic and in 45 cases, clinical evidence support this concept

[This explanation seems to be adequate in some cases but possibly not for the majority Hemic infection of the thoracic skeleton seems to be the commonest route however the age and resistance of patients may have some influence Both mechanisms should be kept in mind because of their bearing on treatment —Ed]

Pleural, Peritoneal and Pericardial Tuberculosis Review of 209 Cases Uncomplicated by Treatment or Secondary Infection is presented by Oscar Auerbach[4] (Staten Island N Y) Most of the patients were between 20 and 39 and 129 were men There were 139 Negroes 68 whites and 2 Asiatics

Tuberculous peritonitis was present alone in 90 and with infection of another serous surface in 41 The preponderance of women (76) was out of proportion both to the number of women in the autopsy series and to the number with serosal tuberculosis Active tuberculosis of some portion of the urogenital system was found in 57 the kidney being involved in 7 and the fallopian tubes in 40 Skeletal tuberculosis was present in 22 almost all of whom had acute generalized miliary tuberculosis Direct extension from the fallopian tubes occurred in 38 from the intestine in 28 and from the pleura in 11 Blood stream dissemination from active extraserosal tuberculosis appeared in 38 Except for the healed primary complex peritoneal tuberculosis was the oldest process in 16 cases In this type a late primary complex may have been the source

Tuberculous pleuritis occurred alone in 55 cases and in combination with involvement of other serous surfaces in 48 There were 84 Negroes and 18 whites a greater proportion of Negroes than in the general autopsy series Associated urogenital tuberculosis was present in 23 and skeletal tuberculosis in 32 The disease was bilateral in 42 and unilateral in the rest Most instances of bilateral disease resulted from hematogenous dissemination whereas direct extension from the lung was responsible for most cases of unilateral infection There was direct extension from the lungs in 35 patients most of whom had chronic pulmonary tuberculosis but in 10 the pleuritis was secondary to a primary complex Peritoneal tuberculosis was the source of direct extension in five cases

(4) Am R v Tuberc 61 845 850 J n 1950

oidin Of the three with disseminated lesions on chest x ray one healed with development of miliary calcification and one with disappearance of the lesion in the third the lesions persisted unchanged for two years before the patient died of causes other than histoplasmosis Figures 42 and 43 show spread of the disease in one of the previously reported cases

Tuberculosis and histoplasmosis were found in two of the original group but in none of the new patients Of the six two had laryngeal histoplasmosis one in whom pre existing torulosis was diagnosed died of periarteritis nodosa and multiple granuloma of undetermined etiology

The combined case material shows variations in diagnostic certainty ranging from clearcut uncomplicated cases of clinical histoplasmosis through the probable cases to those in which the finding of histoplasma was incidental to diagnosis of another disease As the fungus may be found in a wide variety of clinical conditions histoplasma must be suspected in differential diagnosis of granulomatous or infective disease

Recovery of 5 of the 16 patients supports the original concept of the occurrence of nonfatal histoplasmosis as do reports of 9 other proved recoveries in the literature

Studies on Communicability of Histoplasmosis John A Prior and Clarence R Cole[6] (Ohio State Univ) placed five healthy dogs in a kennel with a dog which had a positive reaction to the histoplasmin skin test pulmonary nodules on chest x rays and positive feces and lung cultures for Histoplasma capsulatum Subsequent studies showed no evidence that the organism had been transmitted to the healthy animals In another experiment five healthy histoplasmin negative dogs were placed in cages adjacent to those occupied by eight dogs with spontaneous histoplasmosis After an average exposure period of 7 5 months three had histoplasmin skin reactions In the lesions of two animals H capsulatum was demonstrated and in the third gross and microscopic lesions typical of histoplasmosis were found

Among 25 persons who lived in intimate contact with dogs which had naturally occurring histoplasmosis 16 had definite histoplasmin skin reactions This incidence is little greater than that previously reported for the same region Chest x rays of 18 adult in this group showed pulmonary calcifi

(6) Am. R T be 63 38 46 M y 19 1



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(Co t sy f Furcol w M L I t H lth R p 65 965 994 A g 4 1950)

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(6) Am R Tuber 63 ... 1951

cation in 7 Complement fixation and collodion agglutination tests for histoplasmosis did not reveal evidence of active disease Similar studies on eight laboratory workers exposed to both naturally occurring and artificially induced canine histoplasmosis failed to disclose evidence of active histoplasmosis However the dog should be considered a potential source of infection in view of the fact that the fungus can be transmitted in sputum saliva vomitus feces and urine

[This and the following studies of histoplasmosis presumed or demonstrated help to track down the source of infection in certain geographic areas particularly the rural river valleys The results of infection are usually mild and may vary somewhat with the virulence of the organism Howell and Kipskie (J Lab & Clin Med 36 547 554 October 1950) reported differences in pathogenicity of particular strains The development of a specific stain to detect the organism in tissues was reported at the May 1951 meeting of the Association of American Physicians by Amos Christie Evidence seems to accumulate which suggests that most cases in man are due to inhalation of the organism In two patients lobectomy was performed by Hodgson Weed and Clagett (J A M A 145 807 810 Mar 17 1951) to remove involved pulmonary tissue —Ed]

Simultaneous Nonfatal Systemic Histoplasmosis in Two Cousins is reported by Warren E Wheeler Valerie Friedman and Samuel Saslaw[7] The patients 5½ and 8 lived near Columbus O in a rural area considered endemic for histoplasmosis The clinical and laboratory features did not differ significantly from those in previously reported fatal cases Blood cultures were positive for Histoplasma capsulatum on the sixth and sixteenth hospital days respectively Therapy consisted essentially in bed rest and a diet similar to that for tuberculosis patients None of the antibiotics or chemotherapeutic agents used contributed significantly to recovery

Histoplasma infections in children are characterized usually by fever lymphadenopathy hepatomegaly splenomegaly and massive pulmonary infiltrations followed by minor symptoms An intradermal reaction may suggest past or present infection with H capsulatum In this respect the histoplasmin skin test is comparable to that with tuberculin A positive complement fixation reaction in a dilution of 1 40 or more or a 4+ collodion agglutination reaction in a dilution of 1 10 or greater may be presumptive evidence of active infection The histologic picture in the lymph nodes and occasionally in the bone marrow may permit definite diagnosis by biopsy Proof comes from isolation of the organism from blood bone

(7) Am J D Ch ld. 79 806-819 M y 1950

marrow sputum gastric washings or from biopsy material

Geographic Distribution of Pulmonary Calcification among University Students in Ohio John A Prior John W Wilce *and* William Palchanis[8] *(Ohio State Univ) studied* records of 4 829 students who had had preliminary histoplasmin and tuberculin skin tests and satisfactory chest films on admission None had been absent from his native county for more than four years and only 640 were farm residents

In intradermal skin tests with 0 1 cc histoplasmin in 1 1 000 dilution and 0 1 cc tuberculin (PPD) containing 0 0001 mg a reaction consisted of 5 mm or more of induration at 48 hours Routine 70 mm chest x rays were taken when the skin tests were applied

Rates for histoplasmin reactors and calcified pulmonary lesions differed according to a definite geographic pattern throughout the state The histoplasmin reactor rate highest (77 9 per cent) in the southwestern portion gradually decreased across the state and reached a minimum of 16 9 per cent in the northeastern corner Among students from farms 60 6 per cent were reactors and among nonfarm residents 47 per cent Distribution of pulmonary calcification closely paralleled geographic distribution of histoplasmin reactors but did not correspond to that of tuberculin reactors Incidence of pulmonary calcification about 20 per cent in the southwestern corner of the state diminished gradually to about 5 per cent in the northeastern corner Prevalence of tuberculin reactors was highest in the most highly industrialized areas (15 20 per cent) and lowest in the agricultural areas (11 per cent) Prevalence of both histoplasmin reactors and pulmonary calcification was higher in rural than in urban areas

Although many calcifications are undoubtedly due to tuberculosis these observations support the concept that most pulmonary calcifications in midwestern states probably result from a benign widespread form of histoplasmosis or an antigenically related agent or agents

Disseminated Pulmonary Calcification Report of 114 Cases with Observations of Antecedent Pulmonary Disease in 15 Individuals is presented by F Clark White and Harry E Hill[9] (Ray Brook N Y State Tuberculosis Hosp) Of

(8) P b H lth R p 65 1132 1138 S pt 1 1950
(9) Am. Rev T b 62 1 14 J ly 1950

the 95 males and 19 females 94 per cent lived in a valley region and 84 per cent in a rural environment 78 had been exposed to the dust of threshing and the barnyard Chest x rays showed miliary calcification in 49 and multiple bilateral calcification in 65 Calcific deposits were found in one or both hili in 59 Physical signs and symptoms were infrequent in those whose disease was in the calcific stage There were 11 patients with disseminated pulmonary calcification in four family units Seventy nine persons reacted to histoplasmin and 44 to tuberculin whereas 37 reacted to histoplasmin alone 2 to tuberculin alone and 3 to neither antigen

Among the 15 persons with evidence of chronic pulmonary disease preceding the disseminated pulmonary calcification 12 had exposure to excessive concentrations of organic dust immediately before the initial symptoms Persistent bilateral widely scattered abnormal shadows seen in the chest films of all 15 patients were gradually replaced by calcification during the observation period Skin tests in 13 showed that all reacted to histoplasmin and 9 to tuberculin Of nine patients eight reacted to complement fixation tests for histoplasmosis

Such evidence indicates that the pulmonary disease resulting in disseminated pulmonary calcification may be an air borne infection due to Histoplasma capsulatum or an antigenically related fungus

Outbreak of Primary Pulmonary Coccidioidomycosis in Los Angeles County, Calif, is reported by Morton D Kritzer Marjorie Biddle and John F Kessel[1] (Univ of Southern California) Three febrile patients with respiratory complaints subsequently determined to have primary pulmonary coccidioidomycosis were hospitalized All were members of a group of 61 boys in a forestry camp Serial skin and complement fixation tests with coccidioidin x rays and correlation of physical findings disclosed four additional cases During this study 45 boys transferred from another camp served as controls

When correction for residence was made 29 per cent of the study group but only 7 per cent of the controls were found to react to coccidioidin In the study group about a third of the reactors showed conversion from negative to positive during the study These findings were regarded as adequate evi

(1) Ann I t M d 33 900 990 O tobe 1950

dence of the endemicity of this area in Los Angeles County for coccidioidomycosis The fact that 17 per cent of the study group reacted to complement fixation tests whereas no re actions were observed in the controls furnished additional evidence that the cases represented an outbreak of active coccidioidomycosis Serial complement fixation tests showed conversion of equivocal reactions to positive reactions in five clinical evidence corroborated the diagnosis of active infec tion Further investigation showed that the original hospital ized patients were all members of a road crew which had worked in a canyon during the month preceding the onset of illness

The importance of residence in an endemic area has been emphasized in the literature and corroborated in this study but areas of endemicity have not been worked out completely Since the symptomatology is nonspecific reliance for diag nosis must be placed on serial x rays serial complement fixa tion tests and repeated skin tests In the presence of a perti nent *geographic history accompanied by upper respiratory* infection the first useful diagnostic procedure is the skin test (1 100 dilution) If the reaction is negative the 1 10 dilu tion is used In most primary cases one of these dilutions will cause a positive reaction In patients with allergic mani festations (erythema nodosum) the 1 1 000 dilution should be used To establish a base line of activity a complement fixation test is done At the same time or after a complement fixation reaction sputa and gastric washings are cultured for the organism Several specimens should be obtained for this purpose Concomitantly blood tests and a sedimentation *rate determination should be done and chest x rays taken* Eosinophilia is suggestive evidence of the disease In follow ing the course of the disease greatest reliance is placed on subsidence or recrudescence of symptoms serial x ray changes and results of serial complement fixation tests the last two being the most useful A rising complement fixation titer signifies impending increase in severity of the disease A drop in titer does not necessarily accompany clinical im provement

The primary disease is usually self limiting Symptoms quickly respond to nonspecific symptomatic care Since man *to man* transmission of this disease has not been reported

bed rest at home can be carried out successfully and at less expense to the patient

[The endemicity of this infection has been demonstrated repeatedly and this is a particularly good study —Ed]

Pulmonary Mycoses Coccidioidomycosis and Pulmonary Cavitation, Study of 92 Cases *is presented by* William A Winn (Springville Calif) These cavities varying in size from 1 to 14 cm were associated with hemoptysis in 65 per cent of patients Otherwise there were minimal signs and symptoms In a fourth such cavities existed for months or even a few years and then closed spontaneously In 10 per cent pulmonary cavitation persisted over a number of years without evident harm In 6 per cent the cavity filled and formed a persistent nodule In 2 per cent spontaneous pneumothorax followed transpleural rupture of the cavity with and without empyema

About a third of cases either because of excessive bleeding or increasing size of the cavity demanded closure by pneumothorax or pneumoperitoneum Such measures effective in 18 cases failed in 10 Some smaller cavities with x ray evidence of fairly thick or firm walls were excised intact Larger cavities demanding segmental lobular resection lobectomy or even pneumonectomy were successfully treated in 14 patients

In no case was fatal dissemination of disease observed from a residual pulmonary cavity There was no evidence of transmission of coccidioidal disease from one person to another even when the mother with disseminated disease remained at home with her children

[This is an unusually thorough and comprehensive report of the natural course of this pulmona y disease It is noteworthy that in the localized pulmonary form with cavities bronchial dissemination to other parts of the lungs is not common in contrast with tuberculosis It would seem reasonable in most cases to observe the disease until the full extent of natural healing can be determined or anticipated.—Ed]

Cryptococcosis Review of Literature and Report of Case with Initial Pulmonary Findings are made by Harold E Ratcliffe and Walter R Cook[3] (Brooke Gen l Hosp San Antonio Tex)

Man 30 showed x ray evidence of a pulmonary lesion (Fig 44) *Sputum cultures revealed budding cells with halo like capsules* morphologically characteristic of Cryptococcus neoformans White

(2) A M A A ch I t Med 87 541 550 Ap I 1951
(3) U S A m d Fo es M J 1 957 969 S pt mbe 1950



Fig 44.—C cumscr bed dense filt on pe th l portu f ght m d lung 6 ld (Court y f R 1ff H E nd Cook W R U S Armed F M. J 1 9 7 969 Septembe 1950)

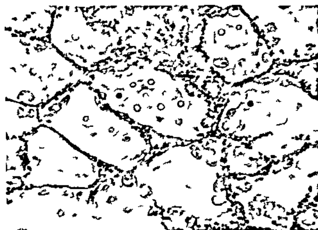


Fig 45.—I l l yeastl ke g m w h h ter t lea p le ote foamy ll along l eol septa (Cou te y f Ratl ff H E nd Cook W R U S A med F M J 1 957 769 Septembe 1950)

mice given intraperitoneal injections of washings from the cultures died within eight days Skin tests for histoplasmosis and tuberculosis and complement fixation and precipitin tests for coccidioides gave negative results but result of a skin test for coccidioides was 3 + There was no cross reaction between cryptococcus and coccidioidal serologic tests He remained completely asymptomatic for almost three months then complained of a slight dull headache. Spinal puncture three days later showed initial pressure to be 200 mm and cell count 8 India ink smears of cerebrospinal fluid revealed yeast like organisms morphologically characteristic of C neoformans Despite treatment with sulfadiazine potassium iodide penicillin streptomycin and polymyxin meningitis progressed and he died about 3½ months after hospitalization

Sections of a firm gray nodule 4 × 5 cm from the middle lobe of the right lung revealed a peripheral zone in which the alveoli contained numerous round to slightly oval thick walled organism with a broad capsule (Fig 45) The meninges from the cerebral cortex to the cauda equina were infiltrated by moderate numbers of organisms

In localized pulmonary involvement in the absence of systemic spread the involved lobe should be removed

[The cryptococcus is a common organism which produces disease only occasionally It has sometimes been observed to cause lesions in patients debilitated by other conditions such as Hodgkin s disease —Ed]

Mucor Mycosis of Lung J D Murphy and S Bornstein[4] (Oteen N C) describe findings in the second case of pulmonary mucor infection reported in this country Both patients were farmers

Man 40 had complained of colds easy fatigue dyspnea anorexia slight weight loss cough and left chest pain for about one year X rays showed a solitary focus in the upper lobe of the left lung The sputum contained no acid fast bacilli The condition did not improve x ray findings remained unchanged and about two years later thoracotomy was performed A round hard mass 3 cm. in diameter was removed from the posterior portion of the left upper lobe On cross section it was yellowish white with concentric layering and near the center there was a dry caseous area Cultures and inoculations of guinea pigs with crushed material from the mass disclosed no evidence of tuberculosis A wet preparation in lacto phenol showed structures resembling septate fungus hyphae and sporangia Cultures on Sabouraud s medium yielded a growth of white aerial mycelium The mold was identified as Absidia italiana a species close to A corymbifera Septation of the hyphae was regarded as a degenerative change Recovery was uneventful

(4) A n I t. M d 33 442 453 A g t 1950

Pulmonary Artery in Bronchiectasis Walter G Gobbel Jr Joseph Gordon and George J Digman (Ray Brook N Y State Tuberculosis Hosp) define the term bronchiectasis as the pulmonary disorder characterized by dilatation of the bronchi and by the pathologic changes in the bronchial wall and adjoining tissues which follow many varied and apparently unrelated conditions such as bronchopneumonia



F g 46 (l ft) —E t n e b on hiect s of left l g R d l nt ea n l ft ppe l g fi ld ep sen f l g h l m ght
F g 47 (c t) —Aft l ng w d d od ed o l njected to pulmo y a te y
F g 48 (ght) —A te iodi d oil was nject d t h h N t xt m deg f br h ect s Dense a at p ph y f l w l b wh h t pe t d b th p lm y arte y o b on h (d t b l ral h matoma wh h d lop d t t me f s t
(Court sy of Gobb l W G J t l J Thora c S g 21 385 390 Ap l 1951)

lung abscess neoplasm and influenza It does not follow bronchial ectasia commonly associated with pulmonary tuberculosis To determine if the pulmonary arteries play a role in the altered function iodized oil was injected into the pulmonary arteries and bronchi of lungs obtained at operation or autopsy X rays were taken after oil was injected into the arteries and after it was injected into the bronchi

(5) J Thor ic S g 21 385 390 Ap l 1951

The pulmonary arteries of normal lungs showed the major branches giving rise to smaller radicles which diminished in caliber as they approached the periphery of the lung The gradual tapering and increased branching of the vessels formed a delicate and uniform pattern The pulmonary artery pattern in bronchiectasis of a nontuberculous lung was the same as that seen in normal lungs (Figs 46 and 47) In tuberculosis the pulmonary artery pattern was greatly altered in the areas of fibrocaseous disease (Figs 49 and 50) Many of the larger branches were short narrowed and irregu



F g 49 (left) —Post o t x y of ch t taken hortly bef d th P t h d fibroca us p lmona y t b cul f t l ft l g After tho copl ty n left d p d to ght l g w th p d ct on of fib oc ous d e s nd cav tati n th gho t upp r h lf f l ng fi ld

F g 50 (ght) —B th l ng nd h a t we e r m d *en bloc* N te mpl te bsen e f b nch f p lm y t y th ghout p phe y f left l g ght upper lobe nd s p gm t f ght lowe l be In right l wer lobe wh ch is l ti ly f e f om d p lm ry t l patt n s n m l

(C rt y of G bb l W G J *et al* J Th ra S g 21 385 390 Ap l 1951)

larly distributed There was a pronounced paucity of the smaller branches in areas of fibrotic disease and complete absence in areas of caseation This pattern was present whether or not there was bronchial ectasia in the tuberculous areas

After resection of the bronchiectatic portion of lung in patients with nontuberculous bronchiectasis arterial oxygen saturation increased This was attributed to removal of poorly ventilated but adequately circulated diseased portions of the lung which acted as a venous arterial shunt mechanism Respiratory physiologic studies support this observation The

absence of circulation in the poorly ventilated areas of fibro caseous pulmonary tuberculosis explain the normal arterial oxygen saturation in pulmonary tuberculosis at rest despite loss of considerable pulmonary tissue

[In some ca es of bronchiectasis there may be an abnormal arterio-venous shunt which would be functionally significant In others ventila tion by way of damaged bronchi may be adequate to supply undamaged alveoli without serious functional effects The distinctions demonstrated by the authors are often significant —Ed]

Congenital Bronchiectasis, Allergic Lung Infiltrations and Situs Inversus Organorum were observed by N Blixenkrone Møller[6] (Univ of Aarhus)

Girl 3 also had chronic catarrh of the upper respiratory tract enlarged adenoids absence of the frontal sinuses strabismu and slight mental retardation There was a history of recurrent pneu monic attacks chronic cough dyspnea and asthmatic attacks these disappeared after lobectomy

The bronchiectasis was considered congenital since ymptoms had been present since birth histologic examination of the removed lobe showed high cylindric epithelium in abnormally wide bronchi and there was a large accumulation of lymphoid tis ue in the bron chial walls Edema fluid and red blood cells in the alveoli were attributed to local sensitization to the bacterial allergens which caused *the bronchiectasis*

[There are a number of reports on this so-called Kartagener tr ad which strongly suggest that the bronchiectasis has a congenital basis Edema fluid and red cells in the alveoli of a resected lobe seem to be explained most often by operative trauma —Ed]

Situs Inversus Bronchiectasis and Sinusitis Report of Family with Two Cases of Kartagener s Triad and Two Additional Cases of Bronchiectasis among Six Siblings W H Bergstrom C D Cook J Scannell and William Berenberg[7] (Harvard Univ) found evidence in the literature to indicate that bronchiectasis occurs in 12 23 per cent of cases of trans position of the viscera This supports Kartagener s hypothesis that hereditary predisposition may be a determining factor in certain cases of bronchiectasis

In a family of father mother and six children two siblings presented the picture of Kartagener s syndrome two had bronchiectasis and sinusitis without dextrocardia and two were normal No history of complicating infectious disease during any pregnancy was obtained from the mother Lobec tomy was required for bronchiectasis in two siblings The traceable relatives of this family presented no significant his

(6) A t b d v 100 161 168 1950
(7) P d t 6 573 580 Oct be 19 0

The pulmonary arteries of normal lungs showed the ma jor branches giving rise to smaller radicles which diminished in caliber as they approached the periphery of the lung The gradual tapering and increased branching of the vessels formed a delicate and uniform pattern The pulmonary artery pattern in bronchiectasis of a nontuberculous lung was the same as that seen in normal lungs (Figs 46 and 47) In tuberculosis the pulmonary artery pattern was greatly al tered in the areas of fibrocaseous disease (Figs 49 and 50) Many of the larger branches were short narrowed and irregu



F g 49 (l ft) —I t o t x ray of best tak n b tly b for de th P tient had fib oc ous p lmo a y t berc l s of nt e left l ng Aft r th a oplasty on l ft d se sp d to r ght l g w th p od t on of fib ocaseo d se and ca t t n th gho t ppe h lf of l g field
F g 50 (r ght) —B th l gs a d he rt w em ed *en bloc* N te compl te b en of b anch f p lmo y a te y th oughout p ph y f l ft l g ght pper lobe a d supe or segment f ght l w lobe In right l w lobe wh ch s relat ly f ee f m d p lmo y rte al p tte n m l
(Cou te y of G bb l W G Jr *et l* J Tho c S g 21 385 390 Ap l 1951)

larly distributed There was a pronounced paucity of the smaller branches in areas of fibrotic disease and complete ab sence in areas of caseation This pattern was present whether or not there was bronchial ectasia in the tuberculous areas

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be removed those in peripheral bronchioles are not accessible Pending re expan ion of a collapsed lobe it was thought that if tl e affected tissue were relaxed by artificial pneumothorax sufficiently to counter the mechanical forces dilating the bronchi permanent atelectasis would be less lil ely to result This measure was instituted in three ca es but though the effect appeared favorable no conclusior s could be drawn

[In acute and subacute pulmonary cc nditions it is difficult and often *impossible to distinguish areas of bronchopneumonia from those* which are partly obstructed edematous a d par ially c llapsed Collapse alone is not known to predi po e to bronchiectasis and the suspe ted mecha nism is usually *infection leading to destruct* v l sions *in* the bronchial wall On the basis of other experience it is doubtful that artificial pneu mothorax would be an effecti e pr ventive measure This article is interesting because of *its comprehen* *s*ivenes and the author s ob ervations —Ed.]

Bronchiectasis in Asthma To evaluate the theory that bronchiectasis often originates from allergic asthma G L Waldbott J M Kaufman and K J Merkle[9] (Harper Hosp Detroit) studied bronchograms of 28 patients with chronic asthma *Bronchography in an allergic patient* i hazardous because of possible asphyxiation by introduction of the oil into an overcrowded bronchial tree sensitivity to the contrast medium or pneumonitis from nonabsorption of the contras material

Definite evidence of irreversible bronchiectasi va noted in four patients in none did the allergic condition appear to be *the* cause of bronchiectasis Wheezing was not typical of that *in bronchial asthma* and *mucus* appeared ea ily with every cough There was *no indication of bronchiectasi* in 15 patients In nine roentgenologists could not agree on the diagnosis x rays showed focal zones of widening of sec ondary bronchi and bronchioles and absence of foliage

Since the 28 patients were selected from 756 per on with chronic asthma it is apparent that irreversible bronchiectasis is rare *in* bronchial asthma if it ever occurs The observations support *DiRienzo s conclusion that bronchographic* changes limited to a portion of the lungs are pathognomonic of al lergic asthma It is also supported by autopsy findings in one case in which only the bronchi of two lobes were filled with thick mucus plugs whereas those in the other lobes showed *only* minor changes It is important to differentiate the e

(9) J All gy 21 339 343 J ly 1950

tory of respiratory disease This horizontal distribution suggests an environmental factor active at the start of embryonic life rather than a genetic factor which should if present become apparent in more than one generation Further investigation of this point is necessary before definite conclusions can be reached However such cases of bronchiectasis probably result from antenatal influences whether they are genetic or environmental Various hypotheses suggest that this congenital abnormality may be an actual structural defect a physiologic failure of the respiratory epithelium a predisposition to infection or an altered secretory activity of the bronchial mucous membrane Others have suggested that in dextrocardia the position of the great vessels may interfere with normal bronchial drainage resulting in bronchiectasis

[Bronchiectasis is seldom demonstrated in stillborn or newborn infants but there is still left the possibility of some congenital defect which later becomes manifest because of developmental anomalies or a predisposition to infection —Ed]

Atelectasis and Bronchiectasis in Pertussis A W Lees[8] (Glasgow) found x ray evidence of atelectasis in 65 of 150 cases of pertussis In all 85 lobes showed collapse of greater or less extent The left lower lobe was involved in 50 5 per cent and the right lower lobe in 36 5 per cent Atelectasis occurred with increasing frequency until the fourth week of illness when incidence declined It seldom lasted longer than five weeks Bronchopneumonia present in 30 of the 150 cases of pertussis had no influence on the incidence of collapse

Extensive pulmonary collapse occurred in six cases Bronchography was performed in four and in all the bronchi in the collapsed area were greatly dilated Of 10 cases with atelectasis of moderate extent slight bronchial dilatation was detected in 4 In 25 cases of pertussis without pulmonary collapse bronchography failed to reveal bronchial dilatation In all cases except one dilated bronchi reverted to normal when the collapsed area re expanded In one case damage was sustained which may lead to progressive disease

Postural drainage or rolling the patient about and percussion over the affected area are useful in treatment of pulmonary collapse caused by aspiration of sputum to the peripheral parts of the bronchial tree Bronchoscopic aspiration is disappointing although mucus plugs in a main bronchus may

(8) B M J 2 1138 1141 Nov 18 1950

identifies some of the common features among which the presence of obstructing mucus is frequently mentioned —Ed]

Bronchi during Asthmatic Crisis Experimental Broncho scopic and Anatomicopathologic Study Pasteur Vallery Radot B N Halpern J M Dubois de Montreynaud and V Pean (Paris) provoked asthmatic attacks in guinea pigs by inhalation of bronchoconstrictors such as histamine and cho line and by inhalation of specific antigens as aero ols after previous sensitization of the animals Postmortem study of the animals with anaphylactic asthma showed considerable edema of the larger bronchi the walls being three to four times normal thickness There were numerous polymorphonu clear leukocytes and definite vascular congestion This edema is considered the essential factor in causing death Animals with asthma due to pharmacodynamic agents showed reduc tion of the bronchial lumen with thickened muscle but no trace of edema Spasm appears to be the essential factor in this asthmatic syndrome In animals with anaphylactic asthma antihistamines prevent edema by virtue of their action on capillary permeability once edema is present however anti histamines are no longer effective In bronchospasm the drugs act directly to relieve spasm

Bronchoscopy was done under pontocaine® anesthesia on seven patients with allergic and six with nonallergic asthma before during and after asthmatic crises No epinephrine was administered Biopsy specimens and sputum samples were ex amined by chemical and cytologic methods Bronchial edema was evidenced by reduction of the lumen with turgescence of the mucosa especially of the spurs This type of edema domi nates the bronchoscopic picture of allergic asthma In non allergic asthma there are hypersecretion of mucus and bron chial spasms but no turgescence to suggest edema These differences were well shown in biopsy material in both the epithelial and the connective tissue layers In patients with allergic asthma antihistamines are of prophylactic value by their action on capillary permeability They are of no value in patients with nonallergic asthma

[Differentiation of broncho pa m interfering with ventilation and the obstructive effects of edema of the mucosa and of secreted mucus is im portant clinically Th s study suggests some of the mechanism which are involved —Ed]

( ) P m d 58 661 664 J 14 1950

lesions from the true cylindric and saccular type of bron chiectasis which is permanent Surgery is not indicated for bronchial changes in asthma since they are benign and reversible

[There seems to be no direct relation between asthma and bronchiectasis although either may develop as an independent complication of the other Patients with bronchiectasis may have extensive chronic bronchitis of a symptomatically asthmatic nature No valid histologic evidence seems to exist which indicates that true anatomic bronchiecta is i a reversible process —Ed]

BRONCHIAL ASTHMA

Sudden Death from Asthma Charles H A Walton D W Penner and J C Wilt[1] (Univ of Manitoba) report 12 cases in which sudden death was due to acute asthma and 1 in which it was due to right heart failure a complication of chronic asthma Observations indicated that there is a characteristic pathologic picture in such cases and that death from bronchial asthma can be diagnosed at autopsy Voluminous lungs mucus plugging prominent hyalinized basement membranes emphysema and eosinophilic infiltration of the bronchial walls were noted in all cases Right heart hypertrophy was present in six but in only one was there clinical evidence of cor pulmonale In four cases the thymus was present but only one showed a generalized increase of lymphoid tissue Splenic eosinophilia observed in all but three cases was conspicuous in most Increased mucus secreting glands and hypertrophy of the bronchial walls were not prominent features Goblet cells were increased in number in seven cases Epithelial metaplasia appeared in only three but was striking Little or no pathologic difference was noted between so called extrinsic and intrinsic cases

Aspirin sensitivity is of poor prognostic import and was manifest in three cases Heavy sedation preceded death in nine suggesting that narcotics may be exceedingly dangerous in an asthmatic Barbiturates may be useful in allaying anxiety but large doses are probably also dangerous

[The clinical and pathologic pictures reported in fatal cases of asthma are often complicated and confused it is therefore difficult to judge the mechanism and the possible means of prevention of death This study

(1) Ca ad. M A J 64 95 102 F bru y 1951

and anticholinergic properties of its most potent component However it is apparently not possible to improve significantly the anticholinergic effect of these agents by using combinations

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EMPHYSEMA

Pathogenesis of Chronic Substantial (Hypertrophic) Emphysema According to Felix G Fleischner[5] (Harvard Univ) the hypothetical assumption that structural changes in the pulmonary parenchyma such as degeneration of elastic tissue initiate development of substantial emphysema is not supported by convincing evidence The anatomic patency of the smaller bronchi and alveolar infundibula contradict the opinion that some kind of bronchial obstruction is the cause but x ray evidence supports it

During inspiration the bronchi are stretched and become longer and wider than during expiration when they recoil and become shorter and narrower The widening and narrowing are almost exclusively passive effects on the bronchial walls produced by the stretching of the lungs and flattening or heaping up of the lining mucosa

In bronchographic studies on bronchial physiology x rays were made during inspiration and expiration in healthy subjects When just enough opaque oil had been injected to deposit a thin lining on the wall of the smaller bronchi in inspiration the bronchial lumen remained patent and permitted free passage of air During expiration the bronchi were shorter and narrower The oil formerly spread as a thin film along the bronchial walls was heaped up the same amount of oil spread over a smaller surface and in several places the oil formed ridges from wall to wall completely filling the lumen In some places the effect of surface tension manifested itself even more by narrowing the bronchial lumen (Figs 51 and 52) This phenomenon is interpreted as the effect of the heaping up of the loosely attached mucosa

Normal respiration with its prolonged expiratory phase compensates for such morphologic mechanical changes but this delicately regulated mechanism may be thrown off balance in any abnormal narrowing which augments resistance

(5) Am Rev T be c 62 45 57 J ly 1950

ACTH Therapy in Bronchial Asthma Histamine and Methacholine Tolerance in Acute Experiment and during Prolonged Treatment J Aaron Herschfus Leon Levinson and Maurice S Segal[3] (Tufts College) studied the action of ACTH in asthmatic patients using the protection study technic Administration of a single adequate dose conferred no protection against the effects of histamine or methacholine The behavior of ACTH was essentially that of an inert substance so far as antihistamine properties were concerned A single dose of ACTH also exerted no beneficial effect on acute paroxysms of bronchial asthma

In additional experiments ACTH was administered daily to each of three asthmatic patients over several days The fall in vital capacity which followed administration of histamine diminished as duration of ACTH therapy increased It was concluded that the abnormal sensitivity of the asthmatic patient to histamine may be lessened or abolished by ACTH

[There have been a number of reports of the beneficial effects of ACTH and cortisone on the hypersensitive state due to antigen antibody reactions Chronic intractable asthma may respond favorably However because the hormones may produce many functional alterations (so-called side effects) sometimes harmful their use in these conditions should usually be reserved for very difficult cases including dire emergencies in which other measures have failed —Ed]

Evaluation of Therapeutic Substances Employed for Relief of Bronchospasm Combinations of Diphenhydramine with Ephedrine and Aminophylline Hyman J Rubitsky J Aaron Herschfus Leon Levinson Elliott Bresnick and Maurice S Segal[4] (Tufts College) studied four sensitive asthmatic subjects in whom a decrease in vital capacity was easily induced by administration of histamine or methacholine Diphenhydramine hydrochloride 50 mg ephedrine sulfate 25 mg and the two agents combined were administered The combined drugs had slightly greater antihistamine activity than did either agent alone but there was no semblance of arithmetic summation A combination of diphenhydramine 50 mg and aminophylline 200 mg had greater antihistamine activity than did either agent alone When diphenhydramine ephedrine and aminophylline were administered together little or no additive effect could be demonstrated In general each combination of drugs appeared to retain the antihistamine

(3) Bull New England M Center 12 139 143 August 1950
(4) J Allergy 21 559 562 November 1950

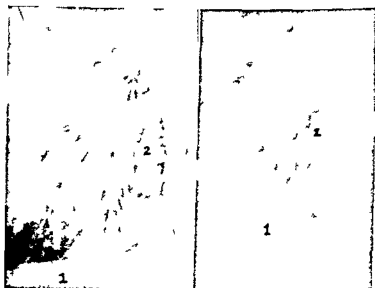
groups based on similarities in the pattern of dysfunction displayed

In the first group are those with pure pulmonary insufficiency who have an arterial oxygen saturation above 92 per cent after the standard exercise test Ventilatory function is more or less severely impaired and there is moderate disturbance *of intrapulmonary air distribution* Adequate alveolar ventilation is maintained by compensatory hyperventilation There is no retention of carbon dioxide The major disability is ventilatory insufficiency Breathing reserve is reduced so that physical activity is limited and dyspnea results Physiologic studies showed moderate increase in total lung capacity and in ratio of residual volume to total lung capacity Maximal breathing capacity was moderately reduced and resting ventilation abnormally large Index of intrapulmonary *mixing* was elevated Arterial oxygen saturation was normal after strenuous bicycle exercise and at rest and arterial pCO_2 was not increased Further evidence of normal over all *alveolar ventilation was increased alveolar pO*

Treatment consists chiefly of measures designed to maintain and *improve* ventilatory capacity *Respiratory infections* should be carefully avoided and vigorously treated if contracted Bronchodilator drugs especially those designed for inhalation may be of great value If the diaphragm is low and greatly flattened vital and maximal breathing capacities may be improved by a well fitting lower abdominal belt Oxygen therapy is not indicated and activity need not be restricted

In the second group are patients with oxygen saturation below 92 per cent and carbon dioxide tension below 48 mm Hg after the standard exercise test In the third group are those with arterial oxygen saturation below 92 per cent and carbon dioxide tension above 48 mm Hg after the standard exercise test The pattern of pulmonary dysfunction displayed by *these groups is essentially similar In some patients* carbon dioxide retention is prevented by compensatory hyperventilation whereas in others carbon dioxide retention occurs In a given patient the level of arterial pCO_2 after exercise may vary from time to time depending on alterations in the degree of bronchospasm In all arterial anoxia is present after exercise but is more severe in patients of the third

during expiration Since increased production of secretions inhibits expiratory emptying in bronchitis and asthma the chest and lung cannot collapse normally Because of impaired hemorespiratory exchange or reflex mechanism hyperpnea may set in causing the successive inspirations to be more forceful and the expiratory phase not properly prolonged



F g 51 (left) —P t n f ght l we l g fi ld bow g bro b l d by th film f op que l (p at n)
F g 52 (right) —Id t l b b (1 and 2) filled by l mns f l t rr pt d by a b bbl s (e p t)
(Cou te y f Fl schne F G Am R T berc 62 45 57 J ly 1950)

resulting in further widening of the chest This labored breathing may lead to formation of greatly dilated alveoli in acute or chronic emphysema

[The obstructive bronchiolar mechanism is extremely important in the development of emphysema and as a cause of ventilatory difficulty Occurrence of bronchitis often due to mild infections may initiate functional disability in patients who previously were able to carry on despite a limitation of respiratory reserve —Ed]

Physiopathologic Aspects of Chronic Pulmonary Emphysema According to John R West Eleanor DeF Baldwin Andre Cournand and Dickinson W Richards Jr[6] (Columbia Univ) patients may be classified into several broad

(6) Am J Med 10 481 496 Ap l 1951

drugs and antibiotics should be used intensively Continuous oxygen therapy should be avoided because of the danger of carbon dioxide narcosis These patients usually have polycythemia and greatly increased blood volumes repeated phlebotomy *is an important factor in therapy*

Pneumoperitoneum in Treatment of Pulmonary Emphysema M G Carter E A Gaensler and A Kyllonen[7] (Boston City Hosp) treated 14 men and 2 women aged 35 74 with far advanced pulmonary emphysema and chronic bronchial infection All were preoccupied with the act of breathing and were apprehensive and intolerant even of minor irritations Dyspnea was the most pronounced symptom in all Three additional patients were treated by pneumoperitoneum after intrathoracic surgery because of complicating emphysema with consequent dyspnea cyanosis and ineffectual cough

The patients were hospitalized and 700 1 000 cc air intro duced into the peritoneal cavity At two day intervals two refills of 500-1 000 cc were given After discharge the patients returned for outpatient refills once every two weeks at which time 80 per cent helium and 20 per cent oxygen mixtures were used

Ten patients spontaneously reported great improvement and 3 moderate improvement Subjective improvement was characterized by reduction in dyspnea increase in exercise tolerance ability to sleep flat in bed when previously unable to do so and ability to raise bronchopulmonary secretions more easily *with consequent reduction of cough* Before treatment average range of diaphragmatic motion in these patients was 10 per cent of normal *after treatment it was 40 per cent* Pneumoperitoneum increased the vital capacity from 1 989 to 2 345 cc and decreased average residual air from 2 677 to 1 980 cc The maximal breathing capacity improved from a mean of 29 L/minute before treatment to 37 L after treatment The walking dyspnea index decreased from 66 to 48 per cent chiefly because of improved maximal breathing capacity No change was observed in the minute oxygen consumption after treatment but the minute ventilation was reduced in all cases

The place of pneumoperitoneum in treatment of early and moderately advanced emphysema is not yet defined The cycle

(7) New England J Med 243 549-558 Oct 12 1950

group Patients in these two groups have alveolorespiratory insufficiency since there is ineffective gas exchange of varying severity in addition to ventilatory insufficiency Physiologic studies showed moderate increase in total lung capacity and striking increase in the ratio of residual volume to total capacity Maximal breathing capacity was greatly reduced Moderate hyperventilation was present at rest Index of intrapulmonary mixing was increased A slight arterial anoxia at rest became more severe on exercise Effective alveolar pO_2 remained normal Treatment is similar to that for the first group except that excessive activity should be avoided Administration of bronchodilator drugs must often be supplemented by other measures designed to improve ventilatory capacity such as abdominal support and breathing exercises Short periods of oxygen breathing several times a day may be of value and may be mandatory when acute respiratory infections gravely impair pulmonary function but care should be taken to avoid habituation to oxygen therapy Since large poorly communicating air cysts may depress ventilatory function surgical removal is often worth consideration in some cases however it is followed by greater impairment of pulmonary function than was present previously

In the fourth group are patients with right sided congestive heart failure and pulmonary insufficiency In contrast with the patients in the other groups there is often lack of compensatory hyperventilation during most phases of activity even in the presence of a fairly large breathing reserve A tendency toward hypoventilation carbon dioxide retention acidosis and arterial anoxia is common Physiologic studies showed reduction of total lung capacity with striking increase in ratio of residual volume to total lung capacity Maximal breathing capacity was extremely small Index of intrapulmonary mixing was greatly increased Arterial oxygen saturation was often low at rest and on mild exercise fell even lower Resting arterial pCO_2 was high and effective alveolar pO reduced Imbalance in alveolar ventilation perfusion relations was extreme as was reduction in oxygen diffusing capacity Ventilatory capacity was greatly reduced making compensatory hyperventilation impossible Treatment includes all measures outlined for the other groups plus additional measures required by congestive heart failure Bronchodilator

bing of the fingers tachycardia and cardiac failure About a third of the patients die a third are seriously disabled and the others recover

Diagnosis depends on an occupational or environmental exposure to beryllium compounds In less than 5 per cent of persons exposed disease develops In severely affected patients oxygen relieves the dyspnea Treatment is symptomatic

Cadmium is extracted from zinc ores and is used in the manufacture of alloys ceramics and cadmium vapor lamps Inhalation of cadmium fumes may cause a feeling of constriction of the chest dyspnea and cough At autopsy there may be hyperemia of the bronchi

Chromium compounds are obtained from basic chromates sodium or potassium dichromate or monochromate Toxicity is determined by valence of the metal radical Dust of chromium salts and mist of chromic acid may produce ulcers on the eyelids or edges of the nostrils The mucous membrane of the nose is commonly affected and perforation of the septum may occur A high incidence of lung carcinoma in the chromate industry has been reported from Germany and the United States but the evidence on which such reports are based is inconclusive Preventive measures include removal of the dust and mist cleanliness regular medical supervision and use of suitable dressings on cuts and abrasions

The most important ore of manganese is black dioxide Manganese is used particularly in manufacture of manganese alloy steel Symptoms and signs of toxicity indicate involvement of the extrapyramidal motor system Some authors have reported an unusually high incidence of pneumonia in men handling manganese ores Inhalation of fumes containing particles of manganese oxides may be associated with an increase in mortality rates for pneumonia Manganese poisoning can be prevented by local exhaust ventilation and careful personal hygiene

Osmium is harmless but the volatile osmium tetroxide osmic acid has an extremely irritating odor and attacks the mucosa of the nose pharynx bronchi and eyes High concentrations produce a sense of momentary constriction of the chest and inability to breathe which may persist for 12 hours Proper ventilation prevents vapors from affecting the workers

Exposure to dusts or spray of complex salts of platinum

of emphysema infection and fibrosis might be slowed in some cases by earlier institution of pneumoperitoneum

[The effect of pneumoperitoneum in these ca es seems similar in some respects to that of wearing an abdominal belt designed to support a pendulous abdomen Stout patients particularly note more effective breathing while wearing the belt Pneumoperitoneum may improve ventilation in some cases but it would not be useful for instance when dyspnea is due to alveolar diffusion difficulty In most cases it seems best first to improve ventilation by clearing secretions from the bronchi and relieving bronchial pasm and edema of the mucosa with inhalations — Ed]

PNEUMOCONIOSIS

Toxicology of Some Metals and Their Compounds Used in Industry is reviewed by Donald Hunter[8] (London Hosp) Occupations involving exposure to beryllium compounds include extraction of the metal from the ore preparation of beryllium steel manufacture and cutting of beryllium copper alloys making of beryllium containing crystals for radio apparatus and coating tubes of fluorescent lamps Symptoms attributable to exposure include conjunctivitis irritation of the upper respiratory tract dermatitis subcutaneous granulomas and acute and chronic lung disease The symptoms of acute lung disease are those of chemical pneumonitis They occur during employment and in the early stages there is cough with blood stained sputum accompanied by retrosternal pain dyspnea cyanosis and weight loss Later dyspnea at rest is noted Rapid respiration anorexia and great prostration follow Death may occur within two weeks Pulmonary alveoli are filled with exudate composed of edema fluid and fibrin containing macrophages When recovery occurs serious sequelae are unusual but acute attacks have been followed by chronic berylliosis after two years Linear marking and ground glass appearance on x ray suggest pulmonary congestion As clinical signs disappear the lung lesions become granular and nodular with conglomerate masses After recovery there is residual fibrosis in some cases Chronic exposure results in vague ill health slight but persistent weight loss weakness and lack of energy There may be persistent upper respiratory tract infection with cough dyspnea club

(8) Brit M Bull 7 5 14 1950

istered intramu cularly four times a day for 28 days Rales gra lually disappeared during the first week Subsequently vital capacity in creased by over 1 L and residual air decreased to within normal range Maximal breathing capacity increased from 55 to 115 per cent of predicted normal value There were decrease in minute ventilation and increase in oxygen absorption at rest X rays showed a gradual decrease in pulmonary markings an apparent decrease in size and density of nodules decrease in size of hilar nodes and clearing of the lungs Symptomatically he was much improved

This case suggests that beryllium granulomatosis may be reversible but follow up studies are necessary to determine duration of improvement

[This and the following two articles report the fir t treatment known to be effective against beryll um granulomatosis The re ults seem to be somewhat similar to tho e ob erved in other granulomatou disease The duration of benefit eems to vary and must be investigated further —Ed]

Effect of Adrenocorticotrophic Hormone (ACTH) on Beryllium Granulomatosis and Silicosis B J Kennedy J A P Pare K K Pump J C Beck L G Johnson N L Ep stein E H Venning and J S L Browne[1] (McGill Univ) administered ACTH in doses of 100 mg daily for varying periods to two patients with beryllium granulomatosis and one with silicosis Results in the two conditions were essen tially similar There was striking subjective and objective improvement with increase in feeling of well being strength and depth of inspiration After cessation of ACTH therapy severe fatigue weakness and spiking fever recurred in those with beryllium granulomatosis Within three weeks after ces sation of therapy one patient had almost reverted to the status before therapy Vital and maximal breathing capacities improved during ACTH administration after cessation of therapy values decreased although they remained higher than originally ACTH specifically affected emotional be havior but the external manifestations varied according to personality type

Metabolic data revealed changes previously reported in patients receiving ACTH Secondary polycythemia was dem onstrated in each patient together with normoblastic hypo plasia of marrow There was also leukocytosis Direct eosino phil count showed a decrease to 0 In all patients urinary 17 ketosteroids during control periods ranged below values

[1] J M d. 10 134 155 F bru ry 1951

may cause running of the nose sneezing tightness of the chest shortness of breath cyanosis wheezing or cough

Exposure to selenium fumes causes immediate and intense irritation of the eyes nose and throat and subsequent un pleasant sour garlic like odor of the breath and body Severe headaches nasal congestion dizziness and redness of the eyes may follow Hydrogen selenide is particularly likely to irritate mucous membranes Symptoms may last for as long as 15 days The garlic like odor of the breath can sometimes be overcome by daily doses of ascorbic acid 10 mg/kg body weight Much smaller quantities of tellurium compounds pro duce a similar odor

Vanadium dust causes chronic bronchitis with cough pro fuse expectoration and sometimes hemoptysis Colds and pneumonia may be more frequent than in the general popula tion

[Taylor (Brit M Bull 7 15 18 1950) has described the toxicologic hazards of some of the newer compounds to which industrial workers are exposed Most of these do *not affect the lungs significantly* and it is interesting that ethyl silicates have not been shown to cause silicosis Other substances which have been investigated include tetrabromoethane which is reported by Gray (Arch Indust Hyg & Occup Med 2 407 419 October 1950) not to produce serious pulmonary effects and allethrin and pyrethrins which are said by Carpenter and associates (Arch Indust Hyg & Occup Med 2 420 432 October 1950) to be of the same relative order of toxicity and safe for use as insecticides in sprays and aerosols —Ed]

***Effect of Adrenocorticotrophic Hormone (ACTH) on* Beryllium Granulomatosis Preliminary Report** B J Ken nedy J A P Pare K K Pump and R L Stanford[9] (McGill Univ) note that *remissions in beryllium granulomatosis* have not followed use of other agents, and regression such as that demonstrated in their patient is unlikely to be spontaneous

Man 27 was formerly employed in a fluorescent lamp manufac turing plant where he was exposed to beryllium dust About four years after exposure he noted cough dyspnea on exertion anorexia and weight loss which continued until first seen 2½ years later Re spiratory studies showed considerable reduction of maximal breath ing capacity and vital capacity Arterial oxygen saturation was low There was polycythemia. Chest x rays showed prominent lung markings diffuse lung infiltrations with micronodular densities and enlarged hilar nodes

He was placed on a constant diet After a 2 week control period during which balance studies were made 25 mg ACTH was admin

(9) Canad M A J 62 426-428 May 1950

(e g after the week end break) and complains of dyspnea fatigue and sometimes cough Within 24 hours he has completely recovered The second stage is characterized by gradual progression of the initial symptoms Symptoms cease when there is no longer exposure to the dust In the third stage tightness of the chest and effort intolerance are present every day and are so severe that the worker may have to give up his job If he leaves the industry progress of the disease is retarded but effort intolerance remains as a permanent injury The essential lesion is emphysema and bronchitis may or may not be present

There are no characteristic x ray changes in byssinosis The causative agent is unknown and its mode of action obscure

Of 103 men over age 35 who had been exposed for at least 10 years to dust in carding and blowing rooms of mills spinning raw cotton 38 per cent had no symptoms 52 per cent symptoms of early byssinosis and 10 per cent disabling byssinosis Susceptibility appeared to have no relation to other respiratory diseases The most recent mortality rates given by the Registrar General indicate an excessive mortality from respiratory and cardiovascular diseases for such personnel over age 55 as compared with other cotton workers and all men over the same age Since the terminal stage of byssinosis may be one of congestive cardiac failure mortality from this disease is probably significant

Although byssinosis can be prevented this has not yet been done successfully Since the second decade of the present century much has been done to reduce the concentration of dust in carding rooms by fitting the stripping brush with an exhaust by vacuum cleaning and by removing dust from the atmosphere by *air conditioning Great interest has been* aroused by new methods of applying oil emulsion to raw cotton to suppress dust A recent investigation showed that of 35 men working in carding and blowing rooms 16 complained of tightness of the chest Within three months after oiling was introduced 8 of the 16 were symptom free

[It is generally su pected th t d lcterious effects of exposure to organ c dust such as cotton a e el ted to a hypersensitive state created by antigens from the material it elf or from contam nations such as bacteria Medicolegally byssinosis mu t be carefully distingui hed from emphysema and bronchitis due to common infections —Ed]

observed in normal adult males Response to therapy varied but in general there were gradual increases Treatment greatly increased glucocorticoids and chemical corticoids Hormone administration was accompanied by retention of sodium chloride with associated fluid retention increased body weight and potassium loss Excretion of urinary sodium and chlorides was decreased There was a tendency for hypopotassemic hypochloremic alkalosis to develop Administration of ACTH increased nitrogen excretion but with sufficient protein in take a negative nitrogen balance could be avoided This re action is similar to that of other patients with chronic debili tating disease

The question as to whether ACTH brings about mobiliza tion of beryllium or increases excretion of the metal was not answered by this study

Repeated short courses of ACTH probably cause fewer complications than prolonged therapy Prolonged cortisone administration may be of value Since there is no adequate treatment for these disorders further investigation of this type of therapy is indicated

Chronic Beryllium Poisoning (Chronic Pulmonary Granu lomatosis) Preliminary Reports on Four Cases Treated with ACTH are made by H S Van Ordstrand Joseph M De Nardi and Robert W Schneider Heretofore no therapy affording even temporary improvement had been found for progressive and severe cases In these patients therapeutic dosage varied from 60 mg ACTH administered every six hours to 50 mg given daily Maintenance dosage after dis charge was about 20 mg daily There were increase in appe tite and weight improved mental outlook decrease in dyspnea and frequency of coughing paroxysms loss of edema and im provement in chest x rays The one patient who was not placed on a maintenance dose had a symptomatic relapse

Byssinosis in British Cotton Textile Industry According to R S F Schilling[3] (Univ of Manchester) byssinosis is found only among persons preparing and cleaning cotton for spinning The first stage usually appears after the worker has been exposed to cotton dust for 5 10 years He notices tight ness in the chest when returning to work after a short absence

( ) Cl el nd Cl n Q t 18 48 54 J y 1951
(3) B t M B ll 7 52 56 1950

per cent Acid fast stains of 39 biopsy or autopsy specimen and repeated gastric and sputum cultures for tubercle bacilli in 30 cases gave negative results Tuberculin tests gave negative results in 65 per cent

On x rays osseous changes were commonest in the phalanges Lesions of about equal frequency were either localized punched out cystic areas without evidence of surrounding inflammatory reaction or striking alteration of the trabecular structure of the bone with extensive cortical atrophy and resorption A coarse reticulated appearance of the medullary portion of the bone was characteristic X ray appearance of pulmonary lesions is nonspecific Only mediastinal adenopathy was present in 7 in 14 linear strandlike markings radiated fanlike from both hilar areas invariably accompanied by massive hilar adenopathy in 9 there were diffuse changes consisting of widely disseminated bilateral nodular foci evenly distributed throughout both lung fields A combination of the last two patterns was seen in 10 patients Diaphragmatic tenting blunting of the costophrenic angles or pleural thickening was seen in nine

Complications included recurrent spontaneous pneumothorax in two patients and cor pulmonale from encroachment on the pulmonary vascular bed by the granulomatous process in four Posterior synechiae corneal opacities or phthisis bulbi was seen in 5 of the 12 with uveal changes 3 had secondary glaucoma Clinically active tuberculosis developed in 13 patients Of known deaths 10 were related to sarcoidosis and 3 unrelated The disease was progressive in 5 and stationary regressive or completely resolved in 22

Treatment largely empiric is disappointing The natural course is so variable that benefits claimed for any specific agent must be interpreted with extreme caution In six instances deep x ray therapy had no appreciable effect on massive hilar lymphadenopathy Development of pulmonary fibrosis did not seem influenced by periods of bed rest

The cause of sarcoid is unknown The strongest argument against tuberculous etiology is failure in most cases to recover tubercle bacilli Emulsions from sarcoid lesions do not cause tuberculosis when injected into experimental animals Among the strongest arguments for tuberculous etiology is the high incidence of complicating tuberculosis and its frequent cause

SARCOIDOSIS

Boeck's Sarcoid Review Based on Clinical Study of 52 Cases is presented by Edgar Alsop Riley[4] (Bellevue Hosp) The basic lesions are granulomatous epithelioid tubercles which may completely replace the normal architecture of the organ in which they appear Such lesions were present in biopsy or autopsy material from all 44 cases in which such studies were made Presence or absence of caseation necrosis is the one definite criterion which distinguishes sarcoid and tuberculosis on purely morphologic grounds The morphologic appearance of sarcoid is nonspecific and such reactions may be caused by many different agents

Sarcoid is primarily a disease of young adults 29 patients were in the third decade Over 50 per cent were Negro females and total incidence among Negroes reached almost 80 per cent The history was positive in 6 of the 47 cases in which tuberculous contacts could be determined specifically

One of the most characteristic features of sarcoidosis is lack of correlation between severity of symptoms and extent of involvement Only nine patients were completely asymptomatic all others had symptoms at some time and these symptoms appeared to be in proportion to severity of involvement Most complaints were referable to the chest and included sputum which was sometimes blood streaked in 65 per cent cough in 63 per cent and shortness of breath in 42 per cent Weight loss was noted by 51 per cent

The most constant clinical sign was lymphadenopathy noted in all patients at some time The nodes were firm discrete and usually not tender Chest x rays showed involvement in 87 per cent Splenomegaly and hepatomegaly were present in 40 and 37 per cent respectively Skin lesions were found in 25 per cent ocular changes in 29 per cent the commonest site being the uveal tract and osseous lesions usually present in the extremities in 13 per cent Pulmonary involvement was common but the only consistent cardiac finding was tachycardia in 40 per cent Sedimentation rate was elevated in 78 per cent and serum globulin value in 68

(4) Am. Rev Tuberc 62 231 282 September 1950

Cigaret smoking was more closely related to pulmonary carcinoma than pipe smoking. There was distinct association with inhaling.

Taken as a whole, lung carcinoma patients had begun to smoke earlier and had continued longer than the controls, but the differences were small and not statistically significant. Fewer lung carcinoma patients had given up smoking.

The possibility was considered that the results could have been produced by selection of an unsuitable group of controls, by patients with respiratory disease exaggerating their smoking habits or by bias on the part of the interviewers. These possibilities were all excluded, and it is concluded that smoking is important in causation of pulmonary carcinoma.

Relative risks among different grades of smokers were calculated. The figures obtained are admittedly speculative but suggest that over the age of 45 cancer risk increases in simple proportion with the amount smoked and may be about 50 times as great among those who smoke 25 or more cigarets a day as among nonsmokers.

A simple time relation cannot be deduced between increased consumption of tobacco and increased number of deaths from pulmonary cancer. This may be because part of the increase is apparent, i.e., due to improved diagnosis, but it may also be because the carcinogen in tobacco smoke is introduced into the tobacco during cultivation or preparation. Greater changes may have taken place in the methods involved in these processes than in the actual amount of tobacco consumed.

Tobacco Smoking Habits and Cancer of Mouth and Respiratory System. Clarence A. Mills and Marjorie Mills Porter[6] (Univ. of Cincinnati) obtained positive information on the smoking habits of 254 Cincinnati patients and 503 Detroit patients with cancer of the respiratory tract or buccal or pharyngeal tissue. They concluded that the percentage of cigar and pipe smokers is almost twice as high among white males with buccal cancer as among appropriately selected controls. There was no significant difference in cigaret smoking habits between patients with buccal cancer and controls. The association of buccal cancer and cigar and/or pipe smoking has been noted often in the literature and has been

(6) C Re 10 539-54 September 1950

of death The case against tuberculous etiology would be stronger were it not for the fact that under certain conditions the pathologic response to virulent tubercle bacilli in both experimental and naturally occurring disease in man may be indistinguishable morphologically from sarcoidosis Investi gations should be directed to study allergy and resistance to the tubercle bacillus in these patients

[In an interesting and significant study of the epidemiology of sar coidosis Michael *et al* (Am Rev Tuberc 62 403 407 October 1950) found that most of 350 patients were born in southern rural districts In view of the unknown etiology of the disease the possible implications were di cussed Israel *t al* (ibid pp 408 417) reported that 20 pa tients with sarcoidosis who were vaccinated with BCG failed to develop skin sensitivity to tuberculin This anergy appears to be nonspecific due to interference with general immunologic mechanisms An elaborate argu ment for a relationship with tuberculosis is given by Leitner (Tubercle 31 174 183 August 1950) On the other hand Bjornstad (Acta tuberc scandinav 24 15 29 1950) suggested that tuberculin anergy indicates that some hitherto unknown chronic infection causes an increased re sistance to tuberculosis This reasoning was ba ed on the finding of calcium shadows in 22 per cent of 71 tuberculin negative patients with sarcoidosis and a history of exposure to tuberculosis in some patients without conversion of kin sensitivity —Ed]

NEOPLASMS

Smoking and Carcinoma of Lung Preliminary Report In England and Wales during the last 25 years the annual number of deaths from lung cancer increased from 612 to 9 287 roughly 15 fold Richard Doll and A Bradford Hill[5] (London) report on 1 732 patients with cancer of the lung stomach and bowel and 743 controls Of 649 men and 60 women with pulmonary carcinoma 0 3 per cent of the men and 31 7 per cent of the women were nonsmokers Correspond ing figures for the controls were men 4 2 and women 53 3 per cent Of the lung carcinoma patients who smoked 26 per cent of the men and 14 6 per cent of the women gave as their most recent smoking habits before illness the equivalent of 25 or more cigarets a day whereas in the control group only 13 5 per cent of the men and none of the women smoked as much Similar differences were found when comparisons were made between maximal amounts ever smoked and estimated total amounts ever smoked

(5) B t. M J 2 739 748 Sept 30 1950

dustry 11 in the chrome pigment industry and 2 in other industries Duration of exposure was 4-47 years Average duration of employment in the German chromate producing group was 22 years Most workers became ill while still employed in the industry or within a year after leaving but there were some whose exposure ended many years preceding the diagnosis of cancer Most authors agree that the compound responsible for the highest incidence of lung cancer is the monochromate since no cases have been reported from the various industries using dichromates Most tumors in chromate workers are bronchogenic carcinomas although a few have been in the upper respiratory tract Except that lung cancer in chromate workers in the United States occurred in a younger age group characteristics did not differ in any significant manner from those in patients in general with lung cancer Chronic irritation has been regarded by some as the mechanism responsible for the carcinogenic property of chromate dust Others have suggested that chromate compounds may act on some of the naturally occurring chemicals in the body in such a way that carcinogenic agents result

Incidence on Basis of Hospital Records —Baetjer[9] reports that of 290 males with confirmed lung cancer at two Baltimore hospitals 11 had a history of exposure to chromium compounds This incidence was regarded as statistically significantly higher than would be expected on the basis of control hospitalized groups Further analysis showed that there were more chromate workers in the cancer series than would be expected on the basis of the number of chromate workers employed in the Baltimore area These data confirm the general opinion that the number of deaths due to cancer of the lungs and bronchi is greater in the chromate producing industry than would normally be expected

Tracheal Aspiration Additional Method for Early Diagnosis of Carcinoma of Lung Preliminary Report William G Cahan and Hollon W Farr[1] (Memorial Hosp New York City) used the method in 42 patients 19 with firmly established diagnoses

METHOD —After the nose oropharynx nasopharynx hypopharynx and subglottic areas are anesthetized with a DeVilbiss power spray containing 1 per cent pontocaine* a no 14 or 16 F

(9) A b I d t Hyg & O p M d 2 505 516 N mbe 1950
(1) C 3 4 5 480 M 1950

attributed to the more sluggish combustion and greater irrita tive tarry materials in these forms of smoking Among pa tients with cancer of the respiratory tract from the larynx downward there is an abnormally high percentage of cigaret pipe and/or cigar smokers In this group the percentage of all forms of smoking is significantly increased

In the present series 93 per cent of all patients with cancer of the lower respiratory tract but only 90 per cent of those with cancer of the upper tract were smokers This is the first study to offer an indictment of all forms of smoking for cancer of the respiratory tract The percentage of non smokers among white males with respiratory tract and buc cal cancer is only a fourth as high as among properly selected control groups

Lung Carcinoma in Iceland Basing his studies largely on autopsy statistics from various countries Niels Dungal[7] (Univ of Iceland) concurs with most authorities in the belief that the last few decades have seen an actual and considerable rise in incidence of pulmonary carcinoma in most countries although incidence in Iceland has failed to show a correspond ing rise In all countries including Iceland there appears to be a preponderance of lung cancer in males Among factors possibly pertinent to increased incidence respiratory infec tions influenza and tarred roads have been present in Iceland during the past few decades but with no apparent change in incidence of lung cancer Statistics on tobacco consumption in various countries suggest that the increased incidence of lung carcinoma is related to increased consumption of cigarets especially between World Wars I and II In Iceland however cigaret smoking did not increase until World War II when it rose enormously Assuming that 20 25 years of tobacco smok ing is needed to produce cancer of the lungs Dungal predicts a considerable rise in the incidence of lung carcinoma in Ice land in 1960 65

Pulmonary Carcinoma in Chromate Workers—*Review of Literature and Report of Cases*—Anna M Baetjer[8] (Johns Hopkins Univ) found 122 reported cases of cancer of the respiratory tract among workers exposed to chromium com pounds Of these 109 worked in the chromate producing in

(7) La t 2 45 247 A g I 1950
(8) Ar h I d st Hyg & O cup M d 2 487 504 \ be 1950

liability can be obtained by rigid adherence to carefully de termined cytologic criteria of malignancy In every case the cytologic diagnosis should be based on precise morphologic criteria alone without aid of clinical information Sensitivity of the cytologic method depends directly on the degree of technical efficiency in collection of material and preparation of smears Since sensitivity of the procedure increases distinctly with the number of specimens examined at least five sputum specimens should be studied Patients with nonmalignant chest diseases should be included in all series as controls and to obtain a broad experience and familiarity with the many pos sible variations in cells from different types of pathologic con ditions Follow up of all patients to final diagnosis is essential if errors in cytologic diagnosis are to be recognized and cor rected and over all efficiency of the technic properly evalu ated A negative cytologic diagnosis does not rule out lung cancer Extensive experience is the most important single factor for with development of skill both the reliability and the sensitivity of the method will improve

Combination of Carcinoma of Lung and Pulmonary Tu berculosis E Attinger[3] (St Gallen Switzerland) studied 759 autopsied cases of pulmonary tuberculosis (450 in males) and 89 of lung carcinoma (72 in men) Only those in patients over age 30 were used in the statistical evaluation 168 cases of tuberculosis were thus excluded Both diseases were present in 12 cases and in most of these the diseases had a close topo graphic relation Age incidence paralleled that for carcinoma alone

Three factors are cited to exclude pulmonary tuberculosis as the decisive etiologic factor in carcinogenesis (1) the high incidence at autopsy of juvenile pulmonary tuberculosis with out carcinoma (2) a similar age incidence of lung carcinoma with and without pulmonary tuberculosis and (3) a much higher ratio of men having both diseases than could be cal culated from the ratio for each disease separately

However the topographic relation indicated that lung car cinoma may occur on a tuberculous basis Three types were differentiated the cavity carcinoma (three cases) carcinoma of the drainage bronchus (three cases) and carcinoma in a tuberculous scar (1 case) Clinically carcinoma of the drain

(3) O l g 3 140 16 1950

rubber catheter is passed through the nose and vocal cord into the trachea A small amount of dilute solution of pontocaine® and saline is dropped slowly into the trachea through the catheter and the catheter then advanced by stages down to the region of the carina Introduction into the right or left main stem bronchus may be at tempted by rotating the patient s head sharply to the contralateral side The bronchus is irrigated and aspirated repeatedly with 2 cc. solution each time until a total of 10 cc has been injected A Clerf cancer cell collector attached to the catheter facilitates this pro cedure When the catheter is removed it is flushed with saline solu tion and the whole specimen mixed with an equal quantity of 95 per cent alcohol and bottled The patient is instructed not to eat or drink for two hours Specimens are then studied by Papanicolaou s method

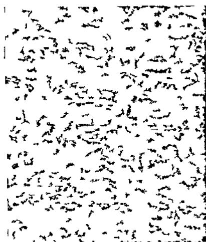
By this procedure there were 11 cases of bronchogenic carcinoma of proved positive classification 5 true negatives 3 false negatives 23 indeterminates and no false positives Cancer cells were somewhat easier to detect because of the relatively smaller number of other cellular types Discomfort and risk of tracheal catheterization are minimal in comparison with bronchoscopy which is costly to both patient and hos pital Tracheal catheterization may be used in patients with pulmonary tuberculosis who produce no sputum and in this way may supplement gastric washings

[Diagnosis based on demonstration of malignant cells in sputum or a pirates by an expert cytologist is usually accurate Failure to demon strate cells however may not contraindicate direct action such as surgical exploration to determine the nature of a lesion strongly suspected to be cancer of the lung —Ed]

Evaluation of Cytologic Diagnosis of Lung Cancer Sey mour M Farber Allen K McGrath Jr Mortimer A Benioff and Milton Rosenthal (Univ of California) examined sputum and bronchial secretions of 2 066 patients by the Papanicolaou and Traut technic Positive cytologic diagnoses were made in 201 cases in 176 tumor was definitely malignant and in 25 it was thought to be malignant Histologic proof of broncho genic carcinoma was obtained in 125 of these patients Of the rest 50 had clinically diagnosed bronchogenic carcinoma 22 metastatic carcinoma to the lung 2 clinically benign chest disease and 2 histologically proved benign conditions

Reliability should be the first objective of cytologic diag nosis A reliable diagnosis is one that justifies surgery in the absence of other morphologic evidence Almost absolute re

(2) J A M A 144 1 4 S pt 1950



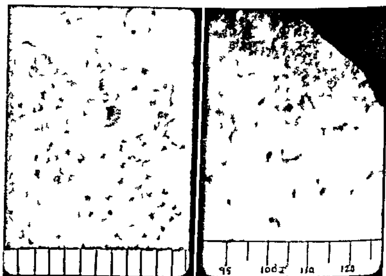


F 55 (t p) —A f l l d th p lmo y d m tos w h dj t orm l l ng bo d ced f m × 96
F g 56 (bottom) —I l d d d f m × 354
(Cou t y f W A B J A h I M d 85 806 818 M y 1950)

age bronchus was characterized by sudden disappearance of tubercle bacilli in the sputum atelectasis and accelerated destruction of the involved lung field In two instances the carcinoma caused an exacerbation of the tuberculous process Prognosis of the diseases in combination is even poorer than that of isolated carcinoma of the lungs

[The coexistence of pulmonary cancer and tuberculosis is observed occasionally in most clinics but the possible etiologic relationship has never been settled conclusively Most investigators believe there is none —Ed]

Pulmonary Adenomatosis Clinical Review and Report of Three Cases, with clinical data from 33 cases previously re



F g 53 (l ft) —Tw 3 mm nod les of p lm ry de matos s o ded by n rmal pulmc y t
F g 54 (ght) —La ge l d t d a ea w th se l small od l bo e (Courtesy f W A B J A ch I t M d 85 806 818 M y 1950)

ported is presented by A B Weir Jr[4] (Memphis Tenn) In the commoner of the gross forms multiple nodules from millet to walnut size are scattered uniformly through the involved portion of the lung less common is the diffuse form which appears as a consolidation of a segment lobe or entire lung (Figs 53 and 54) The involved alveoli in either form are lined by low columnar or high cuboidal cells in one to many

(4) Ar h I t M d 85 806 818 M y 1950

two previous patients may be of definite value in establishing diagnosis

The general types of x ray evidence are (1) multiple small areas of density (Fig 57) and (2) large areas The former may occur as *discrete nodules or irregular and indiscrete areas of* variable size The large areas of density were segmental and lobar and even involved the entire lung X rays did not show hilar adenopathy Pleural fluid was reported in only 3 patients and the site of involvement was bilateral in 27 In general treatment has not been beneficial

Pulmonary Adenomatosis Report of Two Cases Edwin W Peterson and John D Houghton[5] (Veterans Admin Hosp West Roxbury Mass) state that pulmonary adenomatosis is a rare tumor of the lung characterized by tall columnar mucus secreting cells lining the alveolar walls without evidence of bronchial origin or primary adenocarcinoma elsewhere Many theories concerning its origin have been suggested among which are the infectious irritative and neoplastic *Although the neoplastic theory is commonly accepted* there is no agreement as to whether both benign and malignant forms exist

Survey of the literature showed that the disease has been uniformly fatal One of the authors patients was still alive 2½ years after segmental resection and had no clinical or laboratory evidence of recurrence This represents the longest *recorded survival time after surgical attempt at cure It must* be remembered however that symptoms attributed to the disease are reported to have been of as much as eight years duration

Early diagnosis is doubly difficult because bronchoscopy is always noncontributory and cytologic examination of sputum usually gives indeterminate results There is some evidence that the disease is not necessarily multicentric in origin and that early operation may effect cure as it does in any other lung tumor

Pleural Mesothelioma. William N Campbell[6] (Temple Univ) reports 4 cases and reviews 10 from the literature The author s cases represent an incidence of 0 11 per cent among 3 533 autopsies performed in eight years A purely

(5) New England J Med 244 429 433 Mar 1951
(6) Am J Path 26 473 487 May 1950

layers (Figs 55 and 56) Papillary projections and detachment of groups of cells into the alveoli are common Opinions differ as to whether these cells are epithelial or mesenchymal and whether they originate in the alveolar or the bronchial lining

Most of the 56 patients were over 40 Usually no acute illness preceded development of the more or less chronic symptoms of pulmonary adenomatosis Cough was the commonest symptom and usually the first subjective evidence of disease



Fig 57—Small nod l shad ws th o gh t b th pulm n y fi ld de n hl r r g n (Co t y f W A B J A h Int. Med. 85 806 818 M y 1950)

There was a characteristic type of sputum large in volume and clear watery and foamy These signs are compatible with histologic changes since cells are of glandular type Dyspnea was conspicuous and probably resulted from replacement of large areas of respiratory membrane by nonrespiratory epithelium Fever was not uncommon

Of the 17 patients for whom white blood cell counts were given 15 had 10 000 32 000 cells some time during the illness with polymorphonuclear forms as high as 93 per cent. Smears and cultures of sputum were not revealing Bronchoscopy was not an aid in reported cases although profuse bronchorrhea was observed in one instance Aspiration biopsy used on only



Fig 38—P ph l th ac h doe l g ca ma (Court y f F x L W L S A m d F M J l 69 4 M ch 1950)

filling the lumens of a tiny bronchiole This neoplastic tissue was continuous with essentially normal bronchial epithelium and the diagnosis of primary bronchogenic carcinoma was established

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MISCELLANEOUS AND UNUSUAL PULMONARY DISEASES

Blast Injury of Lungs Report of Case Occurring in Peace time Martin Schneider and C P Klein[8] (Univ of Texas) report the only one of eight cases of so called blast injury of the lungs due to the same disaster in which there was no sign of local external or bony trauma to account for the pulmonary lesions

Man 45 stood 100 yd from the French freighter Grand Camp wh n it exploded in Texas City Tex on Apr 16 1947 After the blast he had otorrhea renal and pulmonary hemorrhages The pulmonary hemorrhage progressed for several days egmental atelectasis devel ped and hydropneumothorax appeared Resolution followed w th minimal pleural and pulmonary scarring

Blasts produce a wave of increased pressure which extends radically in all directions with about the speed of sound Velocity duration and magnitude of this pres ure wave at a

(8) R di logy 54 348 353 Ap il 1950

mesenchymal pattern was exhibited by only one case and four presented only an epithelial component The rest presented an epithelial component in some areas and a mesenchymal pattern in others The fact that pleural mesotheliomas usually show a varied cytoarchitecture has been insufficiently stressed The varied structure is readily explained on the basis of embryologic development of the pleura which arises from an epithelial portion of the mesoderm that possesses multipotentialities

Clinical behavior seems the same regardless of cytologic pattern The diaphragm was invaded in 10 cases and the peritoneum studded with tumor nodules in 9 The pericardium was infiltrated by tumor in most cases The characteristic and usual method of spread was by contiguity and serosal seeding Although regional lymphatic metastases and occasional vascular spread have been reported no case provided proved evidence of widespread metastases to parenchymatous organs

If early diagnosis can be established radical extrapleural surgical extirpation with regional lymph node removal may result in cure

Carcinoma of Lung Report of Case Simulating Pleural Mesothelioma is made by Lester W Fix[7] (Great Lakes Ill) The cellular structure was that sometimes described as typical of mesothelioma the clinical picture suggested mesothelioma but autopsy revealed changes which although somewhat characteristic of mesothelioma provided conclusive evidence for diagnosis of bronchogenic carcinoma

Youth 19 had pain in the right chest posteriorly and slight chronic cough for almost one year Chest x rays showed a peripheral thoracic shadow (Fig 58) Exploratory thoracotomy revealed a sheet of tumor investing the right upper posterior lung Biopsy was done and operation concluded because surgical extirpation was impossible The biopsy specimen showed changes compatible with mesothelioma He died about five months later

Autopsy showed a large tumor involving the right third fourth fifth and sixth ribs and extending into the pleural cavity and firmly adherent to and infiltrating into the right lung Dissection of the bronchial tree failed to reveal neoplasm Microscopic study of many sections showed a sharp demarcation between tumor in the visceral pleura and pulmonary parenchyma Study of many more sections finally revealed a 2 mm area of neoplastic tissue almost completely

(7) U S Armed F c M J 1 69 274 M h 1950

opacities with areas of confluence in the inner two thirds of the lung fields (Fig 59) Subsequent x rays showed progressive clearing and by the end of three weeks no significant abnormality

The abnormal shadows were attributed to pulmonary edema This theory is supported by autopsy reports on human beings and animals which have drowned Small areas of associated segmental atelectasis may be a contributing factor

[It is difficult in the e cases to rule out the effects of a piration of vomitus which sometimes occurs In any event the pulmonary irritation and edema predi pose to pneumonia —Ed]

Pulmonary Manifestations of Gasoline Intoxication Review with Report of Case is presented by Reuben Zucker Edwin D Kilbourne and Joseph B Evans[1] (Fort Monmouth N J)

Youth 19 was seen two hours after accidental aspiration of gasoline while attempting to siphon it from an automobile tank Cough and sensation of uffocation were the initial symptoms followed almo t immediately by unconsciousness and dyspnea. Later vomiting occurred making it unlikely that aspiration of gastric *contents was the cau e of the pneumonitis and pleurisy seen on* x rays to be localized in the middle and lower lobes of the right *lung Nonp roductive cough sterile blood culture normal leukocyte* count (the second day) and sterile pleural fluid (the third day) argued against primary bacterial pneumonia Temporary first degree heart block was a novel feature Cough percussion flatness absence of breath sounds and bilateral pleural effusion gradually cleared He was symptom free when discharged about one month later

The predominant manifestations of gasoline intoxication are related to the central nervous system and lungs Dizziness headache coma hilarity and neuritis have been observed If gasoline is in prolonged contact with the skin it may cause desquamation of epithelium or dermatitis When gasoline has been absorbed into the circulation by way of the respiratory *and gastrointestinal tracts histologic study has shown various* changes in the liver kidneys spleen and lungs

Acute Pulmonary Complications Following Inhalation of Chromic Acid Mist Preliminary Observations of Two Patients Who Inhaled Massive Amounts of Chromic Acid are presented by John Boyd Meyers[2] (Seattle)

CASE 1—Man 31 was hosp talized with a history of cough *headache dyspnea and sub ternal pain A week previously* while concentrating chromic acid by boiling it in vats he began to

(1) A h I d t Hyg & O cup M d 2 17 24 J ly 1950
(2) Ib d pp 742 747 Dec mbe 1950

given point depend on the force of the charge and distance from the center of the explosion The initial positive pressure wave is followed by a negative phase of suction of longer duration and less force The hemorrhage seen microscopically throughout the alveoli arises from rupture of dilated capillaries which is attributed to compression of the chest by the positive pressure wave

[Much experimental work was carried out during World War II and the effects of many blast injuries were observed clinically Often there were numerous small hemorrhages in the lung tissue which at first were not clinically manifest but later accompanied by exudative reactions produced severe dyspnea cyanosis and sometimes death of the suffocative type —Ed]

Radiographic Changes in Lungs during Recovery from Drowning are reported by Jerome J Romagosa Leon J Menville and John T Leckert[9] (Charity Hosp of Louisiana)

Man 34 fainted while swimming After immersion for an unknown period he was rescued and artificial respiration administered He later regained consciousness and recovery was uneventful A chest x ray taken about 36 hours after hospitalization showed mottled



Fig 59 —Lung changes 36 hours after immersion. (Courtesy of Romagosa J J et al Radiology 55 517 521 October 1950)

(9) Radiology 55 517 521 October 1950

opacities with areas of confluence in the inner two thirds of the lung fields (Fig 59) Subsequent x rays showed progressive clear ing and by the end of three weeks no significant abnormality

The abnormal shadows were attributed to pulmonary edema This theory is supported by autopsy reports on human beings and animals which have drowned Small areas of asso ciated segmental atelectasis may be a contributing factor

[It is difficult in these cases to rule out the effects of aspiration of vomitus which sometimes occurs In any event the pulmonary irritation and edema predi pose to pneumonia —Ed]

Pulmonary Manifestations of Gasoline Intoxication Re view with Report of Case is presented by Reuben Zucker Edwin D Kilbourne and Joseph B Evans[1] (Fort Monmouth N J)

Youth 19 was seen two hours after accidental a piration of gasoline while attempting to siphon it from an automobile tank Cough and sensation of suffocation were the initial symptoms fol lowed almost immediately by unconsciousness and dyspnea Later vomiting occurred making it unlikely that aspiration of gastric contents was the cau e of the pneumonitis and pleurisy seen on x rays to be localized in the middle and lower lobes of the right lung Nonproductive cough sterile blood culture normal leukocyte count (the se ond day) and sterile pleural fluid (the third day) *argued against primary bacterial pneumonia Temporary first de* gree heart block was a novel feature Cough percussion flatness absence of breath sounds and bilateral pleural effusion gradually cleared He was symptom free when discharged about one month later

The predominant manifestations of gasoline intoxication are related to the central nervous system and lungs Dizziness headache coma hilarity and neuritis have been observed If gasoline is in prolonged contact with the skin it may cause desquamation of epithelium or dermatitis When gasoline has been absorbed into the circulation by way of the respiratory and gastrointestinal tracts histologic study has shown various changes in the liver kidneys spleen and lungs

Acute Pulmonary Complications Following Inhalation of Chromic Acid Mist Preliminary Observations of Two Pa tients Who Inhaled Massive Amounts of Chromic Acid are presented by John Boyd Meyers[2] (Seattle)

Case 1 —Man 31 was hospitalized with a history of cough headache dyspnea and substernal pain A week previously while concentrating chromic acid by boiling *it in vats he began to*

(1) A h I d t H g & Occup M d 2 17 24 J ly 1950
(2) Ib d pp 742 747 Dec mbe 1950

cough and noted wheezing on respiration The cough persisted for two days and became productive of large amounts of greenish mucoid sputum Severe headaches and dyspnea developed the latter persisting even when at rest The chest felt constricted and gradually actual pain developed on deep inspiration In addition to the dyspnea examination showed moderate cyanosis of lips and nail beds and audible wheezing in the chest Pulmonary congestion and edema gradually improved about two weeks after exposure the chest was clear During the eight succeeding months there were chronic cough productive of heavy brownish mucoid sputum and intermittent sharp burning chest pain About seven months after exposure bronchoscopy showed that the mucosa of the entire tracheobronchial tree was hyperemic and somewhat edematous Almost a year after exposure he still had infrequent chills cough and mild chest pain

CASE 2—Man 31 was exposed to chromic acid fumes Three or four days later hoarseness and cough productive of whitish mucoid sputum developed He continued working but became anorexic and noted gradual loss of 20 25 lb About four months later he was hospitalized because of sharp pain in the right upper abdominal quadrant cough and severe chest pain Examination showed splinting of the right side of the chest and a pleural friction rub extending from the midclavicular to the posterior axillary line X rays indicated pleural effusion and subsequent films showed emphysematous changes Almost a year after exposure he still had pain in the region of the former pleural effusion and persistent cough productive of small amounts of greenish mucoid sputum

These cases clearly demonstrate the severe reaction that follows inhalation of massive amounts of chromic acid mist The deeper pulmonary structures are apparently severely damaged although the nasal mucosa is only mildly hyperemic. There was no evidence of hepatic or renal damage in either patient

Chronic Exposures to Air Pollutants and Acute Infectious Respiratory Diseases According to Anna M Baetjer[3] (Johns Hopkins Univ) there is little sound evidence to support the general view that inhalation of dusts and irritant gases may predispose to acute infections of the respiratory tract

A high incidence of pneumonia has been reported among foundry workers exposed to various silica and iron dusts but this may usually be attributed to the sudden chilling which these workers undergo Although coal miners are exposed to carbon dust the recorded rates for acute diseases of the re

(3) Arch Ind st Hyg & O p M d 2 400 406 O tob 1950

spiratory tract vary considerably In rats exposed to silica feldspar cement aluminum or coal dusts there has been no significant lowering of resistance *to lobar pneumonia* produced by intrabronchial injections of pneumococci type I

Autopsy studies from the Pittsburgh district present conflicting evidence as to the relation between the high incidence of pneumonia and the degree of smoke pigment deposited in the lungs Prolonged exposure to high concentrations of smoke did not lower significantly resistance of rats to lobar pneumonia

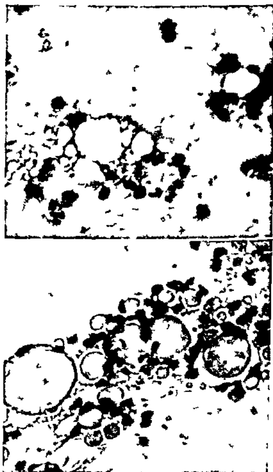
Resistance to acute respiratory tract infections is lowered only by acute exposure to gases and fumes which is *sufficiently severe to damage the mucosa of the respiratory tract* Prolonged inhalation of air containing sulfur dioxide chlorine nitrous fumes and other gases in low concentration probably does not lower resistance to such infections There is no evidence that carbon monoxide either through acute or chronic exposure lowers resistance to respiratory tract infections

[*There is often a tendency to relate acute respiratory infections to irritating dust and fumes but in most instances this does not seem to be justified The etiologic relationships of fatigue, strain and chilling are more important. Excessive smoking does not seem to predispose to acute infections although it may cause irritation of the bronchial mucosa with chronic bronchorrhea.—Ed*]

Pulmonary Paraffinoma (Lipoid Pneumonia) Critical Study Ralph Berg Jr and Thomas H Burford[4] (Washington Univ) report six cases The adult type of lesion usually occurs in older persons who are habitual users of mineral oil orally intranasally or intratracheally Neurogenic and mechanical interference to swallowing may be a factor Mineral oil as such or in one of its medicated forms is the sole etiologic agent There may be no pulmonary symptoms or there may be chronic cough with or without sputum hemoptysis low grade fever *frequent lower respiratory infections and dyspnea on* exertion X ray changes are usually strikingly greater than anticipated from symptoms Clinically and by x ray the lesion is most often interpreted as a primary or metastatic tumor or unresolved pneumonia

On x rays a pulmonary paraffinoma appears as a homogeneous shadow with sharply defined peripheral limits and

(4) J Thora S g 20 418 4 8 S pt mbe 1950



Fg 63 (t p) —L poph g n p t m cu le may be tai ed pos ti e with s d n IV Wr ght t n ed ced f m × 450
Fg 64 (bctt m) —Cl t f l po d-c t ni g ma ph g s and e eral f ee l poid dr pl ts S d IV d d f om × 500
(Co rte y of Volk B W *et l* Am J Med 10 316 324 Mar h 1951)

From the history it was found that 50 patients had taken mineral oil nose drops or oil containing medication over periods of a few weeks to several years Most patients were partially or completely immobilized Fine or coarse rales could be heard over one or both lower lun, lobes in 20 patients

Chest x rays were considered characteristic of lipoid pneu

monia in 20 patients In 10 there was extensive bilateral basal infiltration of varying extent and density The right lower lobe particularly the medial and cardiodiaphragmatic segment was the commonest single site of involvement In the remaining 37 patients the original x rays were not sufficiently characteristic to justify diagnosis of lipoid pneumonia Additional x rays (lateral oblique or overexposed) disclosed considerable retrocardiac and peribronchial infiltration in 13 significant enough to warrant diagnosis of lipoid pneumonia

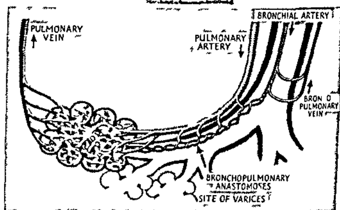
Pulmonary Changes Due to Cardiac Disease with Special Reference to Hemosiderosis A C Lendrum L D W Scott and S D S Park[6] found that in 26 patients with mitral steno



Fig 65—H m d M 38 with m t l t os d m l y h d w th l g wh h ma ed t lly ch g d l ght m th lCou t y f L drum A C t l Q rt J M d 19 249 26 J ly 1950 f om S tt L D W t al B t J R d l 20 100 107 M h 1947)

sis and slight or absent abnormality of the tricuspid valve chest x rays showed miliary shadows in the lung fields (Fig 65) They were attributed to varying degrees of focal deposition of hemosiderin (Fig 66) No hemosiderosis was found in the lungs of five patients with mitral and well marked tricuspid stenosis or in two with mitral stenosis and apparently normal tricuspid valves

(6) Q t J M d 19 49 262 J ly 1950



F g 66 (top) —Lu g sect ons f m 10 pat nts w th h mo d r s a a oc ted w th m tral st Pe ls m th d d ed f om × 1 7
F g 67 (bott m) —A t m r g n f final s uso dal a tomose betwee p l m na y a d b h l c l t
(Co rtesy of Lend m A. C *et al* Q t J M d 19 249- 62 J ly 1950)

Grossly involved lungs had dark bluish spots scattered irregularly over the visceral pleura without relation to lymphatic vessels Gross congestion was noted in three cases Microscopically the nodules were located in the alveolar zones without any obvious relation to bronchi veins or septa The nodules comprised 4-20 adjacent alveoli filled with hemosiderin which was contained in engorged siderophores Each nodule was sharply outlined adjacent air containing alveoli holding few or no siderophores The pulmonary arteries showed varying degrees of the usual changes seen with mitral stenosis and right ventricular hypertrophy Iron was rarely demonstrable in either peribronchial lymphatic vessels or hilar lymph nodes

The intra alveolar aggregations of siderophores were attributed to hemorrhage into the air spaces of the lungs Since groups of adjacent alveoli were stuffed with these cells and alveoli between the deposits were virtually free from them the source of the hemorrhage must have been in the respiratory bronchiole related to the group rather than in the alveoli Such observations indicated that the vessels of the small bronchi the bronchopulmonary anastomoses were the source of the hemorrhage (Fig 67) Other investigators have concluded that frank hemoptysis in chronic cardiac disease is from the same site All evidence indicates that the hemorrhage has a mechanical cause The condition is undoubtedly related to the long standing pulmonary hypertension but may also be seen in patients with systemic hypertension who survive several periods of ventricular failure

A fibrinous type of pulmonary exudate is characteristically seen in diseases giving rise to acute pulmonary edema from left ventricular failure The characteristic form is a cast of the alveolar duct with its related alveoli In three cases osseous masses were attributed to fibrous deposits which escaped ordinary fibrotic organization When the systemic pressure in the bronchial artery falls due to left ventricular failure acute stasis develops in the bronchial pulmonary plexus and if uncomplicated by thrombosis a fibrinous exudate is formed

[This and the following report are among the most carefully detailed and informative articles on the subject that have been published Incidentally the observations suggest some mild granulomatous reaction to siderotic deposits whether of endogenous or exogenous origin —Ed]



F g 68 (top) — Al oli t ffed w th hem de n cont g d ph ges O c d hemal m d ced f m ×18

F g 69 (b tt m) — B o h l ep th l m l w g h m d gr l b tw n n l nd liated b d (b) d al l t g a ma f s d ph g and ome t t t l hemos de (b l w) Perls method d b a l m r d d f m ×585

(Court y of L d m A C J Path & B t 6 555 561 Oct be 1950)

Pulmonary Hemosiderosis of Cardiac Origin At autopsies on 33 patients with mitral stenosis Alan C Lendrum[7] (Univ of St Andrews) found recognizable focal deposits of hemosiderin in 26 Of those without evidence of hemosiderosis six showed no hypertrophy of the right ventricle and in five of these there was concomitant tricuspid stenosis There were four examples of hemosiderosis due to prolonged left ventricular failure in the absence of any valvular abnormality

The histologic picture is the same in mitral stenosis and cardiac failure In a severe case the nodules are distributed in the alveolar tissue and show no obvious relation to main bronchi vessels or septa Each nodule consists of up to 20 adjacent alveoli stuffed with siderophages containing hemosiderin (Fig 68) At the margin of the nodule there is sharp transition from involved to empty alveoli Many nodules show fibrous thickening of the walls of affected alveoli The elastica of arteries in the range of influence of the intra alveolar iron shows slight thickening and gives a strongly positive reaction for iron The hypertrophied spiral musculo elastic tissue of the alveolar ducts also gives a strongly positive iron reaction Rarely giant cell granulomas associated with loss of the alveolar pattern are seen when present they are due to proliferation of the original stromal tissues rather than to organization of alveolar contents Many giant cells contain crystal like structures which give a positive iron reaction Iron positive granules are present in the epithelium of some of the smaller bronchi (Fig 69) and in the secreting cells of some bronchial glands

The focal accumulations of hemosiderin are the end result of hemorrhages from the bronchopulmonary anastomoses in the mucosa of the terminal bronchioles Hemorrhages probably followed distention of anastomoses as a result of raised pressure in the pulmonary arteries In mitral stenosis the pressure increase is absolute and persistent but in cases with remittent left ventricular failure there are periodic falls in the bronchial arterial pressure

Roentgen Studies of Experimental Pulmonary Embolism without Complicating Infarction in Dog Sven Roland Kjellberg and Sten Erik Olsson[8] (Karolinska Inst) anesthetized

(7) J P th & B t, 6 555 561 O tobe 1950
(8) Acta d ol 33 507 514 J 1950

nine dogs and introduced pellets consisting of barium and paraffin 3-4 cm long and wrapped in thin rubber in the external jugular vein The embolus not only obstructed the main pulmonary vessels but because of its soft consistency sent small offshoots into the branches

X rays were made two to four hours after the embolus was at rest No dog showed any x ray changes The vascular design was equally prominent on both sides both before and afterward No local emphysema or other lung changes were seen In one dog into which a contrast medium was injected after introduction of the embolus vessels distal to the embolus were contracted and less prominent than in other portions of the lung Autopsy disclosed no difference in vascularization of the lungs and microscopic examination disclosed no infarcts Branches of the pulmonary artery peripheral to the emboli were not contracted and contained about the same quantity of blood as the other vessels

These observations support the view that no x ray changes can be seen in the lungs in uncomplicated pulmonary embolism Apparently infarction will not occur as long as bronchial artery circulation is undisturbed

[It has generally been assumed that infarction does not usually occur unless the pulmonary circulation has been altered This study seems to support that concept —Ed]

Pulmonary Cavitation Due to Polyarteritis Benjamin P Sandler James H Matthews and Siegbert Bornstein[9] (Veterans Admin Hosp Oteen N C) report a case

Man 39 was hospitalized because of weakness shortness of breath chilly sensations and severe cough productive of thick yellow sputum Diffuse joint pains had developed about nine months and dry cough weakness and dyspnea about one week before admission A chest x ray (Fig 70) showed a large density in the right midlung with an irregular excavation and a thick walled round cavity in the upper lobe There was a solid apical density in the left lung During hospitalization the course was subacute and febrile with increase in secondary anemia anorexia, weight loss and weakness. Additional chest x rays showed multiple cavities and nodular densities with subsequent regression in some areas coincident with progression in others During this time he also had signs and symptoms of nephritis hypertension and gastrointestinal disease and pain in the joints and muscles Terminally there were skin lesions dyspnea became severe renal impairment increased and there was massive hemoptysis At autopsy a diagnosis of periarteritis nodosa was estab-

(9) J A M A 144 754 757 Oct 28 1950

lished There were several large cavitating necrotic regions in the lung and widespread characteristic lesions in other tissues

Periarteritis nodosa has involved the lungs in about 27 per cent of reported cases Pulmonary manifestations may vary considerably Isolated microscopic lesions may be asympto matic and heal without detection Involvement of large arteries may lead to extensive infarction with necrosis and excavation Diagnosis of polyarteritis from a single chest x ray is virtually impossible However if serial x rays show



F g 70 – Ch t film dm (C tesy f S dl B P t l J A M A 144 754 757 O t 28 1950)

regression of earlier lesions and progression of others with or without appearance of fresh lesions the possibility of polyarteritis nodosa should be considered The disease should also be considered when a wedge shaped opacity is seen in the roentgenogram in a case of pulmonary disease of obscure *origin with chronic febrile course and evidence of widespread* systemic disease

[Such necrosis and excavation of the lung do suggest a thrombotic arterial lesion Otherwise the cavity formation might be a sumed to be due to coincidental infect on —Ed]

Pulmonary Fibrosis Following Granulopenia John Friend and A C Thackray[1] (Middlesex Hosp London) report two cases of severe postradiation bone marrow depression compli

(1) La t 2 909 910 D 30 1950

cated by bronchopneumonia which showed considerable organization post mortem The lung changes were considered examples of almost confluent bronchopneumonia as modified by granulopenia and the effects of antibiotic therapy Presence of bacteria and polymorphonuclear cells usually indicates an inflammatory origin of a fibrinous exudate Although few were seen in the lungs in these cases the fibrous exudate was probably not due to noninflammatory conditions Polymorphonuclear cells are generally believed to play a major role in resorption of fibrin during resolution In these cases fibrosis of the lungs could reasonably be attributed to the granulopenia Reduction of granulocytes to levels short of complete agranulocytosis can interfere with resorption of fibrin

As a result of the recent advances in chemotherapy more patients with associated bronchopneumonia will survive long enough for organization to occur in the lungs and for fibrosis of the lung to be recognized as a serious complication of granulopenic pneumonias

[This is an interesting concept which seems reasonable With the increasing survival following pneumonia there seems to be an increasing incidence of pulmonary fibrosis —Ed]

Thrombophlebitis Secondary to Acute Respiratory Infection Robert S Wallerstein[2] reports three cases which illustrate the relatively frequent occurrence of acute thrombophlebitis in young healthy active persons In two thrombophlebitis developed two to three weeks after a relatively mild respiratory infection This experience suggests that too little attention is paid to the causal relation of acute thrombophlebitis to a preceding acute nonspecific respiratory infection In the third patient inflammation of the nasopharynx and ear drums and x ray evidence of a pneumonic process in the right lower lobe preceded acute thrombophlebitis in the right leg by two weeks Subsequently there was eosinophilia of 26 per cent Allergy due to sulfonamides used for the initial respiratory infection was considered an inadequate explanation The thrombophlebitis gradually subsided but several days after discharge there was evidence of thrombophlebitis in the left leg This case may fall in the category of recurrent idiopathic thrombophlebitis of the type described by Barker who felt that it might be the precursor of thromboangiitis obliterans

( ) J Mt S a H sp 17 176 182 S pt O t 1950

which initially is limited to the venous side of the vascular bed

Pulmonary Hydatid Disease Review of 478 Cases Reported in Louis Barnett Hydatid Registry of Royal Australasian College of Surgeons Norman Waddle[3] (Dunedin N Z) found that males were affected more often than females In most cases first symptoms (see table) occurred between

SYMPTOMS OF PULMONARY HYDATID CYST IN 4/8 PATIENTS

S м тоms	N w Ze la P s %	Austral P ті
Cough	80 0	/2 8
Pain	58 0	46 9
Sputum	50 0	47 3
Hemoptysis	47 0	50 6
Pleurisy	26 7	16 4
Dyspnea	24 5	23 0
Vomica	12 5	16 4
Empyema	2.6	?9
Hydropneumothorax	—	2 4
Latent	6 4	9 0

ages 20 and 30 Hydatid cysts grow most rapidly in children but growth rate varies according to the natural resistance of the host s tissues

Only about 10 per cent also had liver cysts This casts doubt on the common view that the liver capillaries serve as the first hydatid filter Abdominal lymphatic vessels and thoracic ducts may provide a route to the lungs which by passes the portal venous system and liver

Diagnosis is difficult since symptoms usually occur only when there is leakage frank rupture or bacterial infection of the cyst X ray appearances and hydatid complement fixation and Casoni s tests are to be relied on for diagnosis Needle aspiration should never be attempted for severe and dangerous complications may result Eosinophilia has no diagnostic significance

Reaction to either the hydatid complement fixation or *Casoni s test is positive only in about 70* per cent of cases Positive reactions to both tests occur in about 36 per cent Negative results do not indicate freedom from disease For x ray diagno is anteroposterior lateral and oblique views should be available Preliminary induction of pneumothorax

(3) A l & N w Ze l d J S g 19 273 290 M y 1950

cated by bronchopneumonia which showed considerable organization post mortem The lung changes were considered examples of almost confluent bronchopneumonia as modified by granulopenia and the effects of antibiotic therapy Presence of bacteria and polymorphonuclear cells usually indicates an inflammatory origin of a fibrinous exudate Although few were seen in the lungs in these cases the fibrous exudate was probably not due to noninflammatory conditions Polymorphonuclear cells are generally believed to play a major role in resorption of fibrin during resolution In these cases fibrosis of the lungs could reasonably be attributed to the granulopenia Reduction of granulocytes to levels short of complete agranulocytosis can interfere with resorption of fibrin

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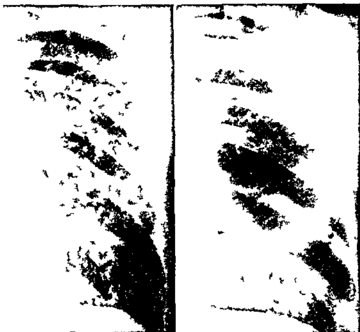
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(2) J Mt S ai Ho p 17 176 182 Sept Oct 1950

drome of a few days duration to a more severe prostrating illness which lasted almost three weeks Extensive laboratory studies failed to reveal a causative agent Postmortem examination of one patient who died of coronary thrombosis five months after the acute illness showed small granulomatous lesions in the lungs and tracheobronchial lymph nodes

In each case a chest x ray taken five to seven days after



F g 71 (l ft) —P t t w exp d f f day h d t f ympt m th d y lat d w ly ll Ch t film th w k fte ympt m pp d how g e ten d sem t d mil ry d
F g 72 (ght) —Th m tb ft t Compl te l g
(Cou t y f F lso B t f Am J R tgen l 64 740 746 N mber 1950)

onset of symptoms showed innumerable finely nodular densities diffusely and symmetrically distributed throughout the lung fields (Fig 71) The appearance was indistinguishable from that of miliary tuberculosis Hilar and mediastinal lymphadenopathy were not apparent X ray changes in the various patients differed only quantitatively In seven lesions

as an aid to x ray study is dangerous since intrapleural rupture of the cyst may result

There were cysts in the right lung in 56 4 per cent in the left in 37 per cent and in both lungs in 6 6 per cent The differences in distribution may depend on the fact that the right pulmonary artery has a more direct course than the left

No systemic treatment destroys the parasite in its host Total elimination of the cyst without spilling any of its contents is the objective This is best accomplished by surgery which should be undertaken early before complications are numerous A fine needle combined with a Fitzpatrick suction bell may be used to reduce the tension of hydatid fluid before removal of the ectocyst but no fluid should be spilled Marsupialization and drainage of the pericyst cavity is the preferred method for handling the bronchial fistulas which are often present or may develop after removal of the ectocyst Formaldehyde should not be used to swab the pericyst cavity Permanent bronchial dilatation usually follows removal of a hydatid cyst but is asymptomatic Gross disorganization of the lung from infection complicating a ruptured hydatid cyst either before or after its removal is the only indication for lobectomy or pneumonectomy

Of 96 patients traced and examined all but 1 of the 21 who had spontaneous rupture and no operation were in good health Of the 40 with uncomplicated cysts treated surgically none died 4 had recurrence in the lungs pleura or scar Of 28 patients who had local removal of complicated cysts 25 were in excellent health and x rays showed no evidence of lung damage All seven with complicated cysts or empyema were well following various methods of treatment

[This is an excellent and unusually comprehensive review of the subject with sound and practical suggestions for treatment —Ed]

Roentgenologic Aspects of Diffuse Miliary Granulomatous Pneumonitis of Unknown Etiology Report of 12 Cases with 18 Months' Follow up is made by Benjamin Felson George F Jones and Robert P Ulrich[4] (Univ of Cincinnati) An unusual illness developed in 12 men 5 14 days after cleaning out an abandoned tower which contained among other things a large quantity of wet pigeon excreta Manifestations varied from a mild transitory grippelike syn

(4) Am J Roentg 1 64 740 746 Nov ibe 1950

pulmonary calcification emphysema or cardiac enlargement

The cause of the epidemic could not be established but three similar epidemics have been reported

[Several endemics of pulmonary disease in people exposed to dust or some other agent in a cave cellar or belfry have been reported which resemble this epidemic A fungus has been suspected but has usually not been demonstrated The permanent fibrosis which results from the organizing character of the lesions seems to be a common residual —Ed]

Pulmonary Infiltration and Blood Eosinophilia in Children (Loffler s Syndrome) Review with Report of Eight Cases is presented by Rosa Lee Nemir Arthur Heyman J D Gorvoy and Edmund N Ervin[5] (New York Univ) Loffler described a syndrome characterized by transitory pulmonary infiltrations eosinophilia and a benign course with few symptoms The allergic nature of the syndrome was stressed and similarity to the pathogenesis of erythema nodosum noted The transient pulmonary infiltrates appeared comparable to a visceral erythema nodosum Later others described patients with more severe symptoms and a prolonged course

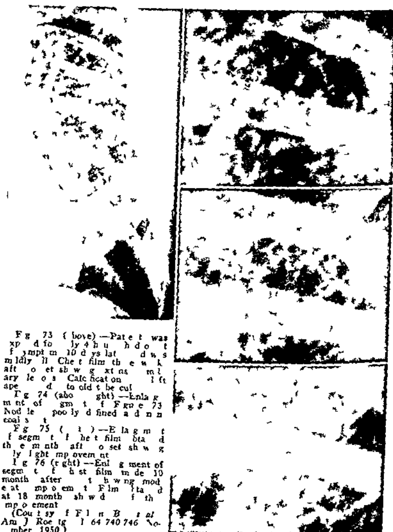
Loffler s eosinophilic pneumonia is apparently an allergic response of the lung to a variety of agents extrinsic such as the privet plant or intrinsic such as helminths and tuberculosis Occasionally the disorder is associated with bacterial infections Experimental pathologic and clinical evidence support the allergic etiology No constant clinical or x ray picture can be associated with any single causative agent

The eight patients in this series illustrate the varied clinical picture associated with Loffler s syndrome In five the course was short and benign with x rays which cleared in 7 18 days Three had a chronic course and showed fine mottling throughout the lung fields which simulated miliary tuberculosis The shadows persisted for 7 weeks to 7½ months

Physical signs were never striking and consisted chiefly of scattered resonant rales Some patients had frank cough expectoration and fever whereas others were symptom free Hepatomegaly was noted occasionally and in three patients liver function tests disclosed liver damage These three also had the most sustained and severe eosinophilia

The most likely provocative allergen in seven patients was an intestinal parasite Tuberculin skin tests gave positive reactions in four but no positive cultures for Mycobacterium

(5) J Ped t 37 819 843 D ember 1950



Fg 73 (bove) —Pat e t was xp d fo ly 4 h u h d o t f ympt m 10 d ys lat d w s m ldly ll Che t film th e w k aft o et sh w g xt ns m l ary le o s Calc ficat on l ft ape d to old t be cul

Fg 74 (abo ght) —Enla g m nt of gm t f F gu e 73 Nod le poo ly d fined a d n n coal s t

Fg 75 (t) —E la g m t f segm t f he t film bta d th e m nth aft o set sh w g ly l ght mp ovem nt

Fg 76 (r ght) —Enl g ment of segm t f h st film m de 10 month after t h w ng mod e at mp o em t F lm ta d at 18 month sh w d f th mp o ement

(Cou t sy f F l n B t al Am J Roe tg l 64 740 746 No- mber 1950)

became gradually less perceptible on successive x rays and ultimately faded Most patients showed complete disappear ance of the miliary densities three to five months after onset (Fig 72) In four progressive but incomplete clearing oc curred 3 weeks to 10 months after onset (Figs 73 76) The process then appeared stationar

DISEASES OF THE PLEURA

Pathology of Pleural Sclerosis Study Related to Loss of Expansivity of Lungs and Its Treatment Oscar C Croxatto and Ruben Sampietro[7] (Univ of Buenos Aires) studied specimens obtained at over 200 autopsies on patients with chronic pulmonary tuberculosis 138 surgical specimens removed in treatment of many conditions and material from experiments on over 100 dog lungs

The stages in formation of pleural adhesions do not differ from those in formation of granulation tissue elsewhere The first stage is fibrinogenesis as a direct result of intervention the second angiogenesis and the third fibrogenesis The inductive period lasts for some hours during which the mesothelium is destroyed In the second stage formation of blood vessels predominates lasting up to 15 days fibrosis complete in 10 more days follows The whole process lasts about 30 days In the third period most vessels disappear but a few remain and occasionally acquire the size of a peripheral artery

The response of pleura varies depending on whether irritation comes from the lung or from the pleural cavity An inflammatory pleural lesion is not indispensable for formation of an adhesion When irritation comes from the lung and is mechanical there is separation of the mesothelium The mesothelium of the parietal pleura is altered and a mechanical adhesion is formed The mesothelium adjacent to the visceral pleural lesions proliferates over the adhesion covering it and forming papillary protrusions Such adhesions do not alter the superficial lamina elastica and their separation does not bring alteration

When the irritation from the lung is inflammatory an adhesion forms its organizing element originating in the parietal pleura The adhesive process extends past the limits of the lung lesions and the lamina elastica is partially destroyed This is important because when such adhesions are freed formation of subpleural emphysema may result

When irritation is external the result is determined by

(7) J Th S g 21 259 274 M h 1951

tuberculosis were obtained Improvement after treatment for the intestinal parasite made the etiologic diagnosis more certain Relapses in two patients were associated with recurrence of ova in stools

The importance of differentiation of tuberculosis from Loffler s syndrome is indicated by the three patients with miliary mottling Characteristics which suggest Loffler s syndrome are well being of the patient absence of splenomegaly absence of other evidence of tuberculous miliary spread striking and persistent eosinophilia and negative cultures for Myco tuberculosis

Factors indicative of allergy other than Loffler s syndrome were found in six patients Pleural exudate was noted in one The transitory character of certain pulmonary x ray shadows is due to atelectasis Loffler s syndrome is not necessarily a benign disease for weight loss or failure to gain in some patients is significant and impairment of liver function may further interfere with health

Pituitous Catarrh Laennec originally described this catarrh in which expectoration is colorless transparent ropy frothy on the surface and underneath like the white of egg diluted with water J V Gordon[6] (Springbank Australia) reports a case

Man 36 for 5 years had been awakened nightly after about 7 hours of sleep by a paroxysm of coughing lasting 30-45 minutes during which 1 1¼ pt sputum was produced During the day he was asymptomatic Physical examination was unrevealing

The sputum fitted Laennec s description perfectly It was acellular and culture revealed no pathogenic organisms Bronchoscopy showed the bronchial mucosa a little redder and softer than normal Extensive secretion was seen coming from all bronchial orifices Biopsy showed extremely active secretory glands of the bronchial mucosa and no obvious inflammation

For two years nocturnal coughing and expectoration had continued therapy was of no avail and the general condition remained good

removed by aspiration with relative ease after injection of SK SD Five patients received one injection the others two or more In those receiving one treatment results were definite and prompt in promoting extensive evacuation of the em pyema pocket ameliorating rapidly the general clinical con dition and terminating the disease In the other patients the first treatment produced favorable results but since final clearing seemed protracted additional injections were admin istered Patients treated relatively early after development of empyema usually required additional treatments and aspira tion In 10 patients decided improvement was evident within the first 48 hours after injection of SK SD Final x ray clear ing was complete within the ensuing two to six months In two patients the enzymes had no appreciable demonstrable effect probably because of cellular organization or other local changes in the tissues which were not subject to liquefaction

In seven cases bacterial cultures of pretreatment samples of empyema exudate were positive After injections of SK SD increased quantities of fluid were obtainable by aspiration and there was striking improvement both clinically and on x rays In four cases cultures rapidly became sterile whereas in two cultures became strongly positive after enzymatic action In these cases enzymes probably uncovered viable organisms hidden in and protected by the exudate Negative cultures probably resulted from entrance of fresh serum and actively phagocyting leukocytes into areas made accessible by appli cation of SK SD

In four cases of postpneumonic empyema injections of en zymes were used in association with closed thoracotomy Re sults were highly favorable as large amounts of exudate were evacuated and re expansion of the lungs was promoted

[Recently attention has been d rected to the use of olutions of pure crystallized trypsin (t yptar) to digest coagulated exudate in the pleura nclud ng that due to tube culous empyema Th s preparation may prove useful although the gn ficance of irr tating effects with fever must be determined — Ed]

Pleural Fluid Eosinophilia F G MacMurray Sol Katz and H J Zimmerman[9] (Washington D C) report three cases

Case 1 —Man 36 had lobar pneumonia The 24th hospital day thoracentesis yielded 70 cc slightly opaque reddish brown fluid con taining 30 000 cells cc other than erythrocytes of which 40 per

(9) N w E gl d J M d 43 330 334 A g 31 19 0

prevention of bronchiectasis means prevention or better treatment of the predisposing conditions particularly pneumonia pertussis pulmonary collapse and so called chronic bronchitis When cough persists after one of these conditions adequate convalescent care coupled with postural drainage and breathing exercises is advocated When bronchiectasis is established beyond doubt a choice must be made between three forms of treatment (1) A cure may be attempted by radical surgical removal of all diseased parts of the lung (2) Treatment may be purely medical with the aim of relieving symptoms (3) If the disease is too extensive for radical surgery excision of the more grossly diseased parts may be combined with medical treatment for relief of symptoms

In general radical surgical treatment is recommended in all cases in which an adequate amount of healthy lung can be preserved In skilled hands the operative mortality in children is low and with the reduction of complications by modern anesthetic methods and chemotherapy operative risks are minimal Medical treatment which can be carried out at home at an open air school or at a convalescent home includes drainage breathing exercises and general health measures Chemotherapy for established bronchiectasis has so far been disappointing Penicillin aerosol in a number of cases produced no lasting effect but more promising results have been reported with combined penicillin and streptomycin

Of 202 patients with proved bronchiectasis followed up to 10 years 109 were treated medically 13 were classified a cured Of 50 patients treated with complete surgical removal 27 were cured In both groups results were much better in patients without asthma Of 19 patients who died 9 had been treated surgically Ten patients classified as cured had bilateral lobectomy

Serial bronchograms taken over the years revealed frequent increase of dilatation in the anterolateral (pectoral) branches of the upper lobes in contrast to improvement or cure of the apical branches Varicose and fusiform types of bronchiectasis produced the least physical disturbance Although clinically established bronchiectasis usually improved in the first two decades it is feared that deterioration may occur in the third and fourth decades The fact that after

of cases were studied (1) 272 cases of pulmonary collapse (2) 99 cases in which diagnosis of bronchiectasis was doubtful at first examination

Pulmonary collapse was seen most frequently in the right middle lobe and left lower lobe It was usually persistent in the left upper lobe but frequently the right lower lobe re expanded Duration of cough from the history was commonly three months or less in cases of pulmonary collapse that re expanded in contrast to two years or more in most cases in which bronchiectasis developed Of the 272 cases of pulmonary collapse in only 157 did the lung re expand without permanent bronchiectatic changes It was not uncommon however to find temporary bronchial dilatation in this group the bronchi returning to normal caliber when the collapse re expanded—a condition described as reversible bronchiectasis

Treatment recommended for pulmonary collapse includes steam inhalations postural drainage and breathing exercises Unless foreign body is suspected immediate bronchoscopy is not necessary No significant difference in incidence of re expansion of the lung was found between the cases treated with bronchoscopy and those treated without Of the 157 children with pulmonary collapse in whom bronchiectasis did not develop 111 were classified as cured with no symptoms or signs after three years observation 16 children were improved and 13 showed no change in general condition In these last two groups 23 children had asthma Six children mostly infants died from associated conditions and the rest could not be assessed accurately Field concludes that in most cases except those with asthma cure was effected

Diagnosis for 99 patients was doubtful bronchiectasis when they were first seen Of these 47 5 per cent had asthma a disease frequently difficult to differentiate from bronchiectasis In 40 true irreversible bronchiectasis developed after three or more years It was necessary to observe patients with doubtful bronchial dilatation over a period of years bronchograms being repeated at intervals to determine the permanently diseased parts

Prophylaxis Treatment and Progress with Follow up Study of 202 Cases of Established Bronchiectasis—Field[6] states that

(6) Ped t cs 4 355 372 S pt mbe 1949

the incidence of bronchiectasis was 65 3 per cent but in those with predominantly exudative lesions it was 19 4 per cent Bronchiectasis in reinfection tuberculosis was most apt to occur after the first year of disease when the lesion had largely lost its exudative quality Extreme chronicity did not increase materially the chance for development of bronchiectasis Predilection was shown for the upper lobes and apical ramifications in lower lobes In contrast to bronchiectasis associated with primary tuberculosis the lingula was frequently involved and in general dilatations were confined to peripheral areas without sharp limitation with respect to bronchopulmonary segmentation In most cases bronchiectasis appeared so limited in extent as to have had little bearing on the clinical course

Unlike primary tuberculosis the factors leading to bronchiectasis in reinfection tuberculosis were less tangible Bronchial occlusion intrinsic factors involving the bronchial wall and extrinsic factors such as parenchymal lesions must be considered

[It is generally agreed that obstruction of a bronchus by a tuberculous lesion may lead to secondary destructive infection with permanent bronchiectasis However there is still much confusion with respect to changes in the bronchi related to uncomplicated parenchymal tuberculosis Some pathologists hold that under these circumstances true bronchiectasis is unusual and that the observed bronchographic defects can be explained as residual cavities or bronchial distortions due to fibrosis —Ed]

Pathogenesis of Bronchiectasis Roentgen Contribution. According to Felix G Fleischner[8] (Harvard Univ) bronchiectasis is a condition characterized by a dilatation of bronchi Inflammation of bronchi lung and pleura and bronchostenosis play etiologic roles but loss of resilience of pulmonary parenchyma in pneumonia and emphysema and shrinking such as occurs with atelectasis and fibrosis provide the mechanical forces which dilate the bronchi Clinical manifestations are determined by the type and severity of complications

Deep necrotizing bronchitis may occur in respiratory infections particularly in children destroying bronchial walls and leading to bronchopulmonary abscesses These if stabilized may be relined with epithelium but if so are not bronchiectatic Dilatation of the bronchi is preceded and ac

(8) Radiology 53 818 833 Dec 1949

lobectomy the remaining lung increases its functional capacity in growing children makes it desirable to operate during childhood

Relationships between Tuberculosis and Bronchiectasis Study of Clinical and Postmortem Material is presented by Edna M Jones W M Peck C E Woodruff and H S Willis[7] (Detroit Mun Tuberculosis Sanatorium) Bronchograms were obtained in 34 children whose mean age was 5½ years Lipiodol® instillation was carried out at a mean interval of 3½ years after x ray clearing of primary pulmonary tuberculosis Definite bronchiectasis was found in 24 in 20 there was evidence of bronchial obstruction for more than one year and in the remainder for less than one year Bronchi were obstructed less than a year in five and more than a year in five of those who had no evidence of bronchiectasis Bronchiectasis was distributed equally between the lungs It was localized in the anterolateral branch of the upper lobe bronchus in nine in the apical branch of the lower lobe bronchus in four and in the middle lobe bronchus in four In every instance bronchiectasis occurred at the site of the previous primary tuberculosis Bronchiectasis tended to be coextensive with the bronchus and cylindric from root to periphery suggesting that anatomic or physiologic obstruction from endobronchial disease at or near the root or from enlarged tracheobronchial lymph nodes may be responsible Symptoms either were associated with the obstruction and primary complex (wheezing fever cough and thick sputum) or resulted from subsequent dilatation (recurrent colds fever cough copious expectoration or hemorrhage)

Postmortem bronchograms in 99 cases of reinfection tuberculosis showed bronchiectasis in 51 instances This diagnosis was substantiated by gross examination and histologic study in 46 All gradations of lesions were found between the extreme of complete bronchial obstruction with a resultant cavity surrounded by caseous material and collapsed alveoli and instances of typical bronchiectasis lined by stratified squamous epithelium showing minimal obstructive changes Most commonly tuberculous disease in the bronchial wall was extensive In cases of predominantly fibrotic disease

(7) Am Rev Tub c 61 387 398 March 1950

to be settled. Overdistention of the lung does not seem to be a direct or important factor in pathogenesis since bronchiectasis has not been observed to develop after lobectomies or pneumonectomies when the remaining lob s or lung may be greatly distended The importance of identifying and treating infections particularly of a suppurative character is generally recognized —Ed]

Frontal Sinuses in Bronchiectasis Study on Morphologic Basis of Lung Disease is presented by Johan Torgersen[9] (Univ of Oslo) The frontal sinuses are smaller in many persons with bronchiectasis than in normal persons and were smaller in a group with congenital bronchiectasis than in a nonselected group Since roentgen abnormalities in the lungs were relatively slight in persons with congenital bronchiectasis examination of lungs and frontal sinuses may indicate the relative role of hereditary and environmental factors in the etiology of an individual case

In a previous article Torgersen dealt with the frequent occurrence of bronchiectasis in persons with situs inversus The most reasonable interpretation of these observations and those described in the present article may be that development of the upper and lower respiratory tracts depends on the integrative action of a complex of genes The manifestation of these genes depends on modifiers influencing the asymmetry of the viscera

Broncholithiasis Herbert W Schmidt O Theron Clagett and John R McDonald[1] (Mayo Clinic) report experiences with 41 patients Sex distribution was about equal and 71 per cent were aged 40 59 Symptoms varied from an unconscious raising of a small stone with a mild cough to severe stone asthma or bronchial colic accompanied by intense substernal pain and a sense of suffocation Multiple broncholiths were coughed up nonsynchronously by 19 patients Cough hemoptysis thoracic pain and fever were the commonest symptoms Physical findings were not diagnostic but depended on the size and location of the broncholith The roentgenologist suspected broncholithiasis in only three cases Probably the most diagnostic x ray sign was a dense area of calcium deposition at the apex of a triangular portion of collapsed lung

Bronchoscopic findings may be suggestive of tumor since often the broncholith is buried in a fleshy mass of granulation

(9) A ta d 1 3 185 192 1949
(1) J Th S g 19 226 245 F bru ry 1950

companied by infection in most cases but is often mild and sometimes entirely absent Such findings do not in any way explain why bronchi become widened

In rare instances of rapidly developing complete bronchial obstruction with severe infection beyond it the secretion accumulating in the closed bronchi may contribute to bronchial dilatation by pressure from within However known physical and physiologic facts do not generally support the concept that secretion in the bronchi and differences of gas pressure within the bronchi and the surrounding parenchyma have a dilating influence

Loss of extensibility of the parenchyma occurring with patches of pneumonic consolidation or emphysema may cause an increased external dilating pull on the bronchi because of loss of the normally well balanced cushioning effect of the resilient parenchyma In atelectasis and fibrosis with shrinkage an outward contractile strain is added augmenting the pathologic traction on the bronchial wall Impairment of normal ventilatory expansion and collapse are the basic mechanical disturbances common to these conditions In the early phases the dilating conditions are reversible and when they disappear dilated bronchi may return to normal This concept of the cause of bronchial dilatation explains most of the clinical and morphologic features of bronchiectasis and is well supported by x ray and histologic observations

In treating bronchiectasis the main effort should be prevention of crippling deformity of the bronchi Infection must be combated and residual atelectatic areas reventilated after any respiratory infection especially in childhood X ray evidence of persistent atelectasis even in small areas should encourage use of bronchoscopic aspiration and any other measure to prevent the condition from becoming chronic If respiratory infection is treated effectively pleural and pulmonary complications are recognized early and foreign bodies and bronchial tumors promptly removed the incidence of permanent gross bronchial deformity will be reduced Instances of chronic suppurative disease with extensive bronchopulmonary damage requiring surgery will become less frequent

[It is interesting to read this point of view on the factors involved in pathogenesis of bronchiectasis indicating that the question does not seem

to be settled Overdistention of the lung does not seem to be a direct or important factor in pathogenesis since bronchiectasis has not been observed to develop after lobectomies or pneumonectomies when the remaining lobes or lung may be greatly distended The importance of identifying and treating infections particularly of a suppurative character is generally recognized —Ed]

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(9) A ta d ol 32 185 192 1949
(1) J Th S g 19 226-245 F bru ry 1950

tissue When this tissue is removed by forceps the broncholith may be felt or seen Biopsy is extremely important since broncholiths may occur in association with bronchogenic carcinoma Once the broncholith is removed the bronchial mucous membrane usually returns to normal In 17 cases the broncholith was either found and removed or coughed up immediately after bronchoscopy Hemorrhage or pneumothorax may occur after bronchoscopy but is not usually serious

When the broncholith is in a part of the bronchial tree that cannot be visualized by the bronchoscopist the problem is that of an indeterminate bronchial lesion In such cases early exploration is safest since a large percentage of these lesions have turned out to be bronchogenic carcinomas and not broncholiths If a broncholith is found segmental resection lobectomy or pneumonectomy may be necessary depending on its location In this series it was necessary to remove all or part of a lung in 10 cases There were no surgical deaths Broncholiths may arise from calcified or o sified lymph nodes calcified or o sified elastic cartilage of the bronchi or metastatic pulmonary calcification Of the 10 cases in which the lung was available for study ossified or calcareous cartilages were present in 9 and ossified or calcareous nodes in 5 in 1 there was no calcific change in either the cartilage or the lymph nodes

Bronchoscopic removal or surgical resection usually relieves symptoms

Active Bronchopulmonary Lithiasis Eugene Freedman and James H Billings (Cedars of Lebanon Hosp Los Angeles) report seven cases of active bronchopulmonary lithiasis six were proved by surgery and histologic examination and in the seventh the stone were expectorated This raises to 103 the total number of cases reported in the American and English literature since 1900

Broncholiths may develop outside the bronchi in any thoracic organ which has been the site of necrosis or inflammation followed by calcification Subsequently the stones may perforate into the air passages When forming within bronchi broncholiths may originate from anthracotic or silicotic material inspissated secretions fibrous plugs soft tissue se

(2) Rad 1 gy 53 203 215 A gu t 1949

questra or foreign bodies Salivary calculi rhinoliths tonsil liths or spicules of bone loosened during surgery on the si nuses or nose may be aspirated and become broncholiths Usually broncholiths are due to perforation of calcified tuber culous lymph nodes

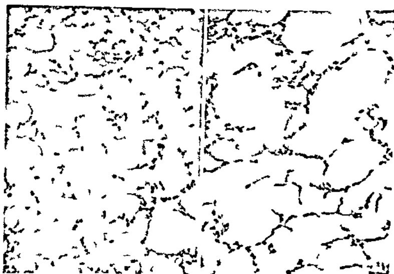
Most broncholiths are from 2 to 20 mm in diameter and are grayish or brownish white Their surfaces may be smooth irregular or mammillated and they are occasionally enclosed in a fibrous capsule They may be solid or laminated and may even contain a liquid center They are composed of 10 15 per cent calcium carbonate and 85 90 per cent calcium phosphate

The clinical picture may vary from absence of signs or symptoms to those of a severe illness The manifestations are manifold and depend greatly on the degree of obstruction and secondary inflammatory changes distal to the obstruction Cough is usually paroxysmal first dry then productive Pain is frequently localized in the parasternal area Hemoptysis is frequent particularly after expulsion of the stone Fever chills leukocytosis and anemia may be present Bronchorrhea is caused by increased goblet cell activity in the irritated mucosa

Bronchoscopy may reveal the broncholith within the bronchi or arouse suspicion of a perforating calculus by re vealing an ulcerating or granulomatous lesion in the bron chial wall However even in the presence of a negative biopsy carcinoma is the condition most commonly suspected Con clusive diagnosis is not possible on the basis of x ray findings These may suggest carcinoma of the lung chronic lung ab scess chronic bronchiectasis with atelectasis chronic pneu monitis or fungoid disease Laminagraphy is an important diagnostic aid for it may show the stone in the bronchial lumen or demonstrate it in close relation to the bronchial wall with secondary inflammatory changes peripheral to the point of obstruction

The broncholith is often expelled spontaneously with characteristic relief of symptoms Removal of broncholiths by bronchoscopy is not without risk of pneumothorax medias tinal emphysema and hemorrhage Lobectomy or pneumonec tomy may be required *The plan of treatment must be based* on the type of pulmonary and vascular complications sec ondary to the bronchial obstruction infection or hemorrhage

Local Organ Hypersensitivity to Autogenous Antigens Experimental Production of Pneumonitis was achieved by Richard Jahiel and Rene Jahiel (Columbia Univ) Lungs of young mature rabbits were sensitized by a single transthoracic injection of a small amount of hydrolyzed autoserum



F g 37 (left) —R ght l g of bb t t d w th 0 5 cc hydroly ed a t serum Shock ι j t on of 2 g x weeks lat Rabb t k ll d 48 h rs ft w d N t al eol ed ma
F g 38 (ght) — l ght r ct n n l ft l g f the s m bb t
(Cou te y f J h el R nd Jah l R J All gy 21 10 119 Ma h 1950)

autogenous urine or saline extracts of homologous liver or autogenous skin Two to 10 weeks later a shock injection of the antigen was given intravenously Then the rabbits were examined over a period of 1 96 hours

Control animals received only intrapulmonary sensitizing injections Focal congestion and edema which developed in the lung disappeared in 10 15 days Controls which received only intravenous injections had no tissue reactions Those in which the sensitizing injection was given subconjunctivally in

(2a) J All gy 21 10 119 Ma ch 1950

the vitreous humor or in the brain developed lesions in these organs after the shock injection but no pulmonary lesions

Previously sensitized animals which received an intra venous injection of the same antigen after a suitable time interval developed lesions in the sensitized lung during the first hour which were still present 96 hours later The severity of the lesion was not appreciably influenced by the time in terval between the two injections when it was varied between 2 and 10 weeks Lesions obtained with exogenous antigens were identical to those obtained with endogenous antigens Grossly there were areas of congestion and edema which in volved a portion of a lobe to as much as the entire lung de pending on the severity of the reaction Microscopically le sions were located mainly in the blood vessels and alveoli Capillaries in alveolar walls were congested and alveolar spaces contained edema fluid (Figs 37 and 38) Vascular le sions consisted of endothelial reaction endarterial and peri arterial edema and periarterial infiltration with eosinophilic cells and small and large mononuclears The pneumonitis was interpreted as an allergic vascular reaction of the lung involv ing relatively large vessels arterioles venules and alveolar capillaries

These experiments suggest that partial hydrolysis of autogenous protein tissue destruction and liberation of endo cellular material and reabsorption of an excretory product may give rise to autogenous allergens which cause changes in previously sensitized tissue Such mechanisms may play a similar role in man

Parenteral and Aerosol Administration of Antihistaminic Agents in Treatment of Severe Bronchial Asthma Hyman J Rubitsky Elliott Bresnick Leon Levinson George Risman and Maurice S Segal[3] (Tufts College) used diphenhydramine and tripelennamine to treat 15 patients with severe bronchial asthma which was refractory to conventional therapy Clini cal improvement occurred in 10 as a result of significant relief from bronchospasm or prompt restoration of epinephrine sen sitivity following intravenous administration of antihista mines The most favorable results were obtained in those who were histamine sensitive during protection studies The poor est results were obtained in those with obstruction of the

(3) New Engl J Med 41 853 859 D 1 1949

tracheobronchial tree by inspissated mucus plugs in elderly patients with significant and irreversible cardiac and pulmonary disease and in histamine insensitive persons

DOSAGE —Doses ranged from 20 to 50 mg of either agent and were administered at a rate not exceeding 10 mg /minute To avoid chemical incompatibility the drugs were not mixed with solutions of aminophylline After relief of severe bronchospasm patients may be maintained during convalescence with antihistamines administered by aerosol or rectal routes as supplements to other therapy By the aerosol route 2 5 per cent tripelennamine solution either alone or mixed in equal parts with a bronchodilator may be administered in a Vaponefrin nebulizer For rectal instillation 25 50 mg capsules of diphenhydramine may be used puncturing the ends of the capsule before insertion Either drug may be administered rectally in solution

The most common side reactions were drowsiness and dizziness particularly in the upright position but they disappeared gradually in one or two hours Headache transient chilliness nausea fatigue palpitation pallor blurred vision tachycardia and the alert reaction were observed most frequently

Treatment of Status Asthmaticus Richard A Kern[4] (Temple Univ) states that the best treatment is prevention by complete diagnosis and thorough treatment of asthma complications Anything less than complete and lasting relief does not merit satisfaction

TREATMENT —The patient should be immediately hospitalized in a private room The bed should have foam rubber pillows and mattress and cotton or woolen blankets should be covered with cotton sheets There should be no rugs no upholstered furniture no flowers and the room should be provided with filtered air if possible Freshly painted rooms and insecticidal spray should be avoided Relief from asphyxia is paramount and may be accomplished by oxygen given by mask or intranasal catheter For economy oxygen in helium is best given in a tent When the patient is cyanotic and obviously unable to cough up sputum bronchoscopy should be performed promptly Administration of 0 5 cc epinephrine a minute before the bronchoscope *is passed or even while it is in situ stimulates* secretion of a thinner mucus that can be more readily aspirated During the whole procedure 100 per cent oxygen can be given through the bronchoscope

(4) Postg ad Med 7 40 44 J n y 1950

The patient desperately needs rest and this is best achieved by induction of surgical anesthesia Avertin® is preferred since it is nonirritating and easy to give by rectum in a dose of 60 80 mg /kg body weight Ether is second choice and when administered rectally should be given in doses of 150 200 cc of a mixture of equal parts ether and olive oil mixed with an egg beater For a child aged 12 the dose is 100 cc It should be given slowly 1 2 drachms at a time into a cleansed bowel 20 minutes being required for the whole adult dose Since ether is eliminated in the lungs it may cause irritation of the bronchial tubes

Wet lungs are occasionally seen and may be treated by venesection Removal of 250 cc blood rapidly does more good than removal of 500 cc slowly Hypertonic glucose solution given intravenously (50 100 cc of 25 per cent solution or 25 50 cc of 50 per cent solution) may be helpful in such cases

Frequently the patient is dehydrated and starved If the blood sugar level is below 80 mg /100 cc 1 000 cc of a 5 per cent glucose solution should be administered by slow intravenous drip Salt solution should not be given Total fluid intake should be 2 2 5 L daily Intravenous administration is stopped when oral intake is adequate Epinephrine may be given to advantage intravenously in the glucose infusion 2 cc of 1 1 000 epinephrine in the first 60 cc of infusion requiring 30 minutes to run in Thereafter the rate of administration should be only half as fast If given intravenously or parenterally epinephrine should be administered at the rate of 1 minim/minute and never more than 1 minim at a time When epinephrine fails slow intravenous injections of aminophylline may be effective For adults the contents of one ampule containing 0 5 Gm in 2 cc of solvent are diluted to 10 cc with normal saline and injected evenly over 20 minutes For children the dose is 0 006 Gm /kg body weight Doses may be repeated every six or four hours In less severe case or when the attack begins to yield aminophylline may be given rectally either in a suppository or 0 5 Gm dissolved in 30 cc tap water as an enema Papaverine relaxes smooth muscle spasm but does not depress the cough reflex but it must be ascertained that the patient is not sensitive to opium or its derivatives before it is administered Morphine pantopon® dilaudid® codeine and other opiates should never be used in status asthmaticus nor should antihistamines be used

Since infection plays an important etiologic role penicillin can be started promptly in most cases but not before a suitable specimen has been delivered to the laboratory for culture of bacteria and determination of drug susceptibilities If the patient is known to be

sensitive to penicillin or any other antibiotics they should not be used.

Improvement in an attack of status asthmaticus is heralded by better and more lasting effect of epinephrine increased quantity of a thinner sputum and subsidence of fever It may occur gradually or with dramatic speed In less severe but persistent cases of asthma nonspecific protein shock therapy may be used The initial dose of vaccine is 10 25 million typhoid bacilli repeated for as many as *three or four doses with an interval of five days between injections* For best results the fever must rise to 102 104 F and doses may be doubled or further *increased to achieve such a fever Nonspecific* fever therapy must not be substituted for specific treatment and should be reserved for patients in whom avoidable causes of asthma cannot be found

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PNEUMOCONIOSIS

Determination of Range of Particle Size in Silicogenous Dust—*Presentation of Problems*—H Gessner J R Ruttner and H Buhler[5] (Zurich) state that intense silicogenous properties are generally attributed to quartz dust but not always to the other silicic acid modifications and the silicates regarded by most investigators as actually less silicogenous In this study silicogenous dust means not only quartz but also silicates Dust inhalation is presupposed in the development of silicosis particles over a certain size cannot be inhaled or are stopped in the upper air passages by the physiologic defense mechanism All authors agree that only particles under 10 μ are injurious but opinions vary as to minimal size of injurious particles and are based on guesses The question can only be decided by examination of the dust deposited in the lungs

Several specimens of lungs from deceased silicotic patients were available Before examination of the dust particles some portions of dried lung weighing 2 4 Gm were used to determine total ash content and the portion of ash that was insoluble in hydrochloric acid To avoid sintering of the particles in the incandescent method which would have falsified the results of the intended elutriation analysis the dust ma

(5) S hw m d W h h 79 I 41 1 45 D 24 1949

terial was isolated from the tissue by dissolving the fat and oxidizing the insoluble parts with H_2O_2 in sulfuric acid solution and with nitric acid the silicogenous component remained in the test material while the nonsilicogenous components disappeared The authors stress the necessity for systematic examinations of the ash and dust contents and their variations in each portion of the lungs to show the relations between the anatomic changes and the migration and distribution of the inhaled dust in the lung

Results of examination of individual specimens were shown in protocol extracts which included information about the place of employment the rock present there and its chemical composition duration of exposure of the subject and the anatopathologic diagnosis the findings of crystaloptic roentgen and orienting chemical examinations the results of elutriation analyses

Evaluation of Results —Gessner Ruttner and Buhler[6] show that the total ash content in their six cases agreed particularly well with the findings of Gardner and Redlin for a much larger group The silicic acid content of the ash from lungs of three patients with severe silicosis was about 50 per cent of the total ash This average differs considerably from the American average (19 87 per cent) but remains within the total American variations of 0 33 and 62 79 per cent The three silicotic patients died with an average of 5 9 per cent of silicon dioxide while the corresponding average for the American group was 2 19 per cent The extreme values of the three examined patients are 2 8 and 8 8 per cent which are well within those given by Gardner and Redlin (0 02 and 15 43 per cent)

The particle distribution curves of the three cases showed a maximum in the range of 0 9 1 0 $\mu\Phi$ The proportion of larger particles was 60 70 per cent that of smaller particles 30 40 per cent The larger particles found were about 20 μ in diameter in only a small percentage were particles between 10 and 20 μ The question of how particles under 0 5 $\mu\Phi$ behave in the lung cannot be evaluated from the authors investigations because the curves for this range were uncertain however the percentage of particles of this size in the dust is always low

Results of this study show that the composition of par

(6) S hw m d W h sch 79 1 58 1 6 D 31 1949

ticles in the dust reaches a maximum in the range of 1 $\mu\Phi$ and that with increasing size fewer particles are retained in the lungs In the range of 10 20 μ deposition in the lungs stops because the particles are arrested in the upper parts of the bronchial tree In the technical examination of industrial dust to evaluate the danger of silicosis it is imperative to deter mine the quantitative participation of fine particles This re quires determination of the total concentration of the dust (weight of dust/unit of volume of dust containing air) and of its particle composition in addition the chemical and mineralogic composition and especially the quartz content must be studied

Measures to combat dust must take into consideration the finest particles A ventilating system which exhausts the dust containing air and blows in fresh uncontaminated air is best *The use of water to precipitate dust during its formation* (wet boring or polishing) is relatively less effective for fine than for large particles but the decrease of fine particles in the air is still considerable Precipitation of dust already in the air by water sprinkling is generally inefficient The commonly used separators are efficient only for certain particle sizes and the critical limits are usually over 5 10 $\mu\Phi$ rarely under this The result is continuous accumulation of the fine par ticles in the air

[Interest is increasing in the effects of extremely fine particles of dust which may be inhaled especially in certain occupations This obviously is important not only in providing for dust control but also in helping to explain the variety of pathologic changes which may be induced in the lungs —Ed]

Influence of Particle Size on Retention of Particulate Mat ter in Human Lung was studied by J H Brown K M Cook F G Ney and Theodore Hatch[6] (Univ of Pittsburgh) Size is a primary factor in determining the magnitude of the hazard associated with inhalation of particulate matter In this study retention was calculated by direct measurement of the amount of dust returning from the respiratory system in the exhaled air as in the standard procedure for measuring total retention *Each exhalation was separated serially into* several fractions representing air from the upper respiratory tract midportion and alveoli and the amount of dust in each was determined It was possible to calculate the true lung air

(6) Am J P b H lth 40 450 458 Ap 1 1950

in each fraction and the outgoing concentration of dust in upper respiratory air and in lung air From these values and the intake concentration the total retention the one way upper respiratory retention total retention from upper respiratory air and alveolar retention were calculated Essential equipment consisted of a face mask connected to a rotary valve with eight ports for delivering dust laden air and collecting samples The valve was electrically operated through

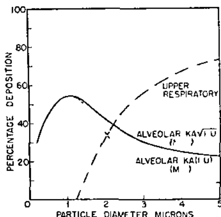


Fig 39—P tag d pos t on f hal d d t th pp p t y t t d l l m l t t p rt l ze (Cou t y f B w J H et l Am. J P b Health 40 450 458 April 1950)

a relay panel and commutator which was connected by a direct mechanical drive to a Drinker respirator in which the person was placed

In over 100 tests with median particle size ranging from 0 24 μ to more than 5 μ total retention decreased systematically from 90 per cent or more for particles 5 μ or greater to 25 30 per cent for 0 25 μ particles Upper respiratory retention also decreased in an orderly fashion reaching zero at a finite particle size above 1 μ Alveolar retention remained at 90 100 per cent for all sizes down to about 1 μ then decreased in proportion to total retention

The percentage of inhaled particles deposited in the upper respiratory tract and in the alveoli were calculated (Fig 39) The alveolar curve is based on the assumption that upper

respiratory retention is equal in both directions For comparison another alveolar curve (dotted line) is given based on assumed one way upper respiratory retention One represents maximal and the other minimal alveolar deposition in relation to particle size The true relationship lies between these two limits Both curves show that for mineral particles the optimal size for alveolar deposition is about 1 μ On a ratio basis probability of deposition is about the same for larger and smaller particles

[Technics of this description are useful in study of the penetration and retention of dust in the lungs and inferentially throw some light on the adequacy of the defenses of the respiratory tract against such penetration —Ed]

Deposition and Fate of Plutonium, Uranium and Their Fission Products Inhaled as Aerosols by Rats and Man. Kenneth G Scott Dorothy Axelrod Josephine Crowley and Joseph G Hamilton (Univ of California) observed the rats in metabolism cages killed them at varying times after exposure to the aerosols and assayed the urines tissues and feces using a Geiger Muller counter and radioautographic technic Particulate material 1 μ or less in size composed of plutonium or uranium or their fission products which include a large series of elements in the central region of the periodic table were deposited in lung alveoli and in respiratory passages lined by ciliated epithelium as evidenced by radioautographs (Figs 40 and 41) Despite the different origin chemical and physical natures of the fissionable and fission products their deposition and elimination were comparable In regions equipped with ciliated epithelial cells almost complete removal of the active particles occurred in a matter of hours but in the alveoli removal of any large percentage of the aerosol required many months Removal was primarily via the bronchial tree and there was no evidence that significant portions were removed by the lymphatic system or blood vessels

The material excreted by the bronchial tree could be detected in the fecal fraction of the excreta Though plutonium and most of the fission products were not absorbed in the gastrointestinal tract recent products of fission such as Ba^{140} Sr^{89} and Sr^{90} were absorbed in amounts of 5 60 per cent of the total given Of the absorbed portion 64 per cent was found deposited in bone The low bone deposition suggests that the

(7) Arch Path 48 31 54 July 1949



F g 40 (top) —L g ect h w g p lmon y d p t f pl t m d os l obta d by b g pl t m bl d d pl ton m t t Th t w k ll d 10 m t ft po Pl t m h ly d p t d cil ted b h l s f d l eol × 6
F g 41 (bott m) —P d tog ph f l g ct × 6
(Court y f S tt K G t l A h P th 48 31 54 J ly 1949)

fission products were locked in insoluble particles when administered as aerosol

[This is an ingenious method of demonstrating the deposition of particulate matter inhaled through the respiratory passages The speed and efficiency with which the ciliary apparatus operates is most remarkable indicating its prime importance as a defensive mechanism Retention of particles in the alveoli for prolonged periods is assumed to be a factor which is largely responsible for inflammatory and fibrotic changes occurring when the material has irritating qualities —Ed]

Aerosols Effect of Saline Aerosols on Dust in Atmosphere, Reduction of Dust Deposition in Lungs by Saline Aerosols L Dautrebande B Highman W C Alford F L Weaver and E C Thompson[8] (U S Pub Health Service) have found that saline aerosols with a mean micellary diameter of less than 0 5 μ can effectively coat and agglutinate dust particles of similar size suspended in the atmosphere To determine the effect of saline aerosols on deposition of dust in the lungs rabbits were exposed for five hours to air mixed with dry willemite dust Another series of rabbits was simultaneously exposed under identical conditions to a similar dust mixed with saline aerosol instead of normal air

Rabbits exposed to the untreated dust generally became sluggish after two hours whereas those exposed to dust treated with saline aerosol remained active even after five hours exposure and showed much less dust in their lungs The first reaction to dust inhalation was short shallow respiration leading to tachypnea Respiratory rate of rabbits exposed to dust alone exceeded 180/minute whereas that of those exposed to dust with aerosol was about 135/minute This difference would be even greater if from the third hour on rabbits subjected to dust alone did not exhibit a certain degree of decompensation of the respiratory centers

Examination showed less pronounced lung changes in the group receiving saline aerosol Dust tended to accumulate at bifurcations of the bronchi and alveolar ducts along surfaces facing the inspiratory current and in the alveoli particularly near the hilus and adjacent subpleural areas When aerosol was not used the lungs often showed many scattered atelectatic areas and the lumens of many bronchi and bronchioles appeared obstructed by exudate intermingled with dust With aerosol these changes were either absent or greatly reduced

(8) Occup Med 5 506-521 M y 1948

Examination of the lungs of animals killed at varying periods after exposure indicated that the dust deposits particularly in the bronchi disappeared after a shorter rest period in the group exposed to the aerosol treated dust

[This is a promising approach to the question of dust control As indicated in the study of Gessner Ruttner and Buhler (p 263) the mere spraying of the air with water may carry down large particles but often leaves finer more harmful particles suspended Some more efficient method therefore is urgently needed —Ed.]

Mortality and Survival Rates in Males with Silicosis or Silicotuberculosis The group studied by H Midgley Turner and W J Martin[9] (Sheffield Univ) consisted of 814 men

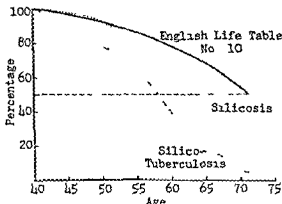


Fig 42—P entag f or f m g 40 d cos d l rub cul (C t y f T H M d Mart W J B i M J 2 1148-1150 N 19 1949)

348 with silicosis and 466 with silicotuberculosis all of whom had reached age 40 Survival rates at ages over 40 for silicosis and silicotuberculosis together with those for the male population are shown in Figure 42 Only 23 cases were first diagnosed as pure silicosis and later as tuberculosis Death occurred in 610 15 cannot be traced and the remainder are living

The ratio of silicotuberculosis to pure silicosis varies in different trades Of 521 grinders 63 per cent had silicotuberculosis whereas of 63 coal miners only 37 per cent had silicotuberculosis Clinical experience supports the view that in comparable cases prognosis is better for coal miners than for

(9) B i M J 2 1148 1150 N 19 1949

grinders it is suggested that the presence of iron in the lungs may have an unfavorable effect on local tissue resistance to tuberculosis

A disadvantage in treatment of silicotuberculosis is that collapse therapy is rarely either indicated or helpful because of the patients ages the almost invariable reduction in cardio respiratory capacity due partly to concomitant emphysema and the difficulty in judgment of the functional capacity of the contralateral lung In men over 50 with silicosis decreased resistance to respiratory infection and the effects of emphy sema and bronchitis on cardiorespiratory function are im portant factors influencing mortality Death from causes other than tuberculosis occurred in 297 patients In 11 per cent death was caused by cancer of the lung Of these 19 occurred in grinders indicating that inhalation of metal dust may be of more importance than inhalation of silica in etiology of cancer

[This study appears to be *highly significant* Up to a certain point silicosis does not cause much functional disturbance Then there may be a rather abrupt and rapid development of disability often related to sim ple respiratory infections to which the silicotic is especially susceptible Subsequently the bronchitis often becomes chronic leading to ventilatory difficulty and increased disability The potentialities of silicosis therefore are serious because of the greater susceptibility to infection whether tuberculous or otherwise —Ed]

"Egg Shell' Calcifications in Silicosis Charles E Gray son and Helen Blumenfeld[1] (Stanford Univ) observed char acteristic calcium densities of unique morphology in the chest x rays of 40 of 200 silicotic men These shadows appeared as circular or oval rings in the hilar or mediastinal regions and there was faint stippling throughout the enclosed tissue Those with calcification had an average of five years less total exposure to silica and a two year longer interval since the beginning of exposure *This suggests that the milder cases of* silicosis occur in those who live longer and therefore deposit calcium many years after the original exposure Sixty per cent of those with calcification and 49 per cent of those without cal cification had no evidence of tuberculosis

Eight patients had a history of exposure to silica and x rays showed shell calcifications and nodular pulmonary densities Silicosis was confirmed by autopsy there was no histologic or clinical evidence of chronic pulmonary infection

(1) R d ol gy 53 16 6 A g t 1949

These findings were regarded as proof of the relation between silicosis and egg shell calcifications Figures 43 and 44 show the typical gross and x ray appearances of such lesions There were no similar findings in lung tissue Apparently calcium deposition begins diffusely throughout the node but



F g 43 (l ft) —T ct d med t nal od
F g 44 (ght) —Roe tg g am f m ll d mm d
(Cou t f G y C E d Ll m f ld H R l g 53 l o A gu t 1949)

later becomes more prominent beneath a heavy capsule that forms around the node

[Pathologists who have had long experience with silicosis are familiar with the difficulty of proving whether or not there are associated changes due to fibroid tuberculosis Though the presence of shell like shadows of calcific density in the lymph nodes is highly suggestive of silicosis particularly when they are numerous and bilateral it seems probable that at least some of them and perhaps a majority are related to associated infection especially tuberculosis which has become partly or completely healed This study is objective and keeps alive the interest in an important problem —Ed]

Morphology of Bauxite Fume Pneumoconiosis J P Wyatt and A C R Riddell[2] (Toronto Ont) report six fatal cases of this disease which is caused by exposure to intense

(2) Am J P th 25 447 465 M y 1949

concentrations of amorphous alumina dust during the manufacture of corundum During the processing of a mixture of bauxite iron and coke in electric furnaces dense white fumes are evolved which lead to contamination of the furnace rooms All fatal cases have occurred in furnace feeders or cranemen

The common clinical findings are shortness of breath cyanosis substernal discomfort and recurrent episodes of spontaneous pneumothorax from rupture of emphysematous



Fig 45 —Al l wall e sw ll n d th k ned by m n l r ell d fit obl t n l nd p ll y p thw v t l t t d × 450 (C t y f Wyatt J P nd R dd ll A C R Am J P th 25 447 465 M y 1949)

bullae Chest x rays show diffuse irregular lacelike and granular shadows greatly increased width of the mediastinum and lung collapse

Analysis of furnace fumes and patients lungs show that both contain significant amounts of amorphous silica and alumina thus offering a close chemical correlation between cause and effect

Grossly the lungs were gray and of relatively normal size on palpation a diffuse widespread induration was noted The size nodulation configuration and granite like character of a silicotic lung was lacking Many large emphysematous vesicles were seen The hilar and tracheobronchial lymph nodes were

not enlarged hard or nodular Microscopic examination of the lungs showed that initially there was intracellular septal edema with early fibroblastic proliferation (Fig 45) Next there was infiltration of inflammatory cells and fibroblastic proliferation was succeeded by collagen deposition The fibrosing septal walls either remained distinct or became massed together and produced wide bands of scar (Fig 46) Obliterative endarteritis was most pronounced in the regions of diffuse

F g 46—Dense b d d t k f ld t d mpby m t p kets X I) (C te y f Wy tt J P nd R ddl A C R Am J P th 25 447 465 M y 1949)

fibrosis There was no evidence of any specific granuloma or sarcoid The tissue reaction did not resemble any previously described process Because of the nature of the history and other findings none of the other pneumoconioses need be considered though in some of the scarred areas doubly refractile particulate matter was demonstrated by Polaroid examination

It is suggested that the mechanism is that of an amorphous dust which evokes a rapid sclerosing process in the pulmonary septa and interferes with the koniophage transmission mechanism usually responsible for dust elimination The

resultant diffuse interstitial fibrosis with absence of nodule formation is probably due to inhalation of amorphous alumina dust though the significance of the simultaneously inhaled amorphous silica has not been completely evaluated

[Identification of this type of pneumoconiosis differing in many respects from classical silicosis opens the field for further investigation of the effects of extremely fine dust It is especially important to recognize that with this disease functional disability appears more rapidly and is of greater severity than with the more familiar nodular silicosis in which lesions are more discrete and fibrosis in the alveolar septa is less diffuse Probably in time some fibroses loosely diagnosed as sarcoidosis will be found to be related to the inhalation of unusual dusts —Ed]

Acute Dermatitis and Pneumonitis in Beryllium Workers Review of 406 Cases in Eight Year Period with Follow up on Recoveries In the series studied by Joseph M DeNardi H S Van Ordstrand and Morris G Carmody[3] dermatologic manifestations occurred in 195 men and 211 displayed major respiratory tract manifestations Of the latter group 121 had tracheobronchitis and 90 chemical pneumonitis Chemical nasopharyngitis invariably preceded these lesions but frequently occurred independently Pneumonitis is the severest form of this industrial disease and 10 patients with this reaction died

The cause of berylliosis has not been established in the plant atmosphere the sulfate and halide radicals and their acids are in relatively greater atmospheric concentration than beryllium In some cases magnitude of exposure was apparently related to occurrence and severity of the disease but in others no such relation could be established Individual sensitivity also contributed to the occurrence and severity of the disease X ray and clinical changes result from irritation arising from the presence of and ensuing reaction to inorganic salts of beryllium in the bronchioles or histamine like by products which cause spasm and partial block of the finer respiratory conduits Exchange of gases in the alveoli is slow resulting in local anoxia which in turn disturbs the colloidal balance in tissues and causes fluids to pour into the alveoli producing edema

The two main types of pneumonitis are the fulminating and the insidious The former is least common and usually is associated with brief exposure to anhydrous beryllium sulfate fumes Symptoms may appear in a few hours or as late as 72

(3) Oh Stat M J 45 567 575 J 1949

hours after exposure and comprise spasmodic cough chest tightness with substernal pain severe exertional dyspnea and in severe cases cyanosis Physical examination reveals acro cyanosis decreased vital capacity limited chest expansion and sibilant rales With adequate care recovery usually occurs within 7 16 days

The insidious type of pneumonitis usually follows pro longed exposure to the fumes or dust of beryllium sulfate tetrahydrate beryllium chloride or beryllium oxide and prob ably results from cumulative irritation of the bronchioles by small amounts of the compounds Symptoms include dyspnea on mild exertion spasmodic cough substernal burning pres sure or pain with tightness in the chest general weakness anorexia and weight loss There are drop in vital capacity acrocyanosis fine to coarse rales rapid pulse and increased respiratory rate temperature is normal unless there is sec ondary infection Complete recovery may require 4-12 weeks

X ray changes in the lungs seldom occur in either type until one to three weeks after onset of symptoms and physical findings Typically peribronchial haziness and punctate in filtration are scattered throughout the lower half of each lung field Treatment for both types consists of hospitalization and intermittent use of oxygen as indicated During the last six months penicillin and the antihistaminic drugs have been given with gratifying results in relief of respiratory distress and spasmodic cough and perhaps have shortened the course of the disease

Recent re examination of 20 persons who had the severer type of pneumonitis revealed no recurrent or chronic manifes tations of the disease and no resultant disability

[The pathogenesis of pulmonary disease following beryllium exposure is still obscure As explained here the mechanisms involved in acute reactions appear relatively simple The granulomatous fo m of reaction is not understood and there is still a question whether complicating infec tion or some other chemical factors may be involved —Ed]

NEOPLASMS AND CYSTS

Fate of Oil Particles in Lung and Their Possible Relationship to Development of Bronchogenic Carcinoma is discussed by L R Sante[4] (St Louis Univ) He reports two cases of bronchogenic carcinoma in one of which the growth undoubtedly arose in pre existing paraffinomas In the other lipoid pneumonia was present but the etiologic relation to the malignant lesion was less definite

After vegetable oil is introduced into the lung that remaining in the bronchial branches is coughed up and expectorated leaving feathery deposits of oil in the alveoli Foreign material in the air sacs cannot be removed by coughing or ciliary action but only by the action of phagocytic cells Microscopic examination shows enormous macrophages surrounding and engulfing oil droplets There is little if any inflammatory reaction probably because vegetable oils are completely free from fatty acids Deteriorated oils should not be used because the fatty acids may result in irritation and lung damage

Animal oils such as cod liver oil cause a mechanical response similar to vegetable oil in the bronchial tree but once they reach the alveoli they remain for long periods before being effectively removed by phagocytosis During this time oxidation and deterioration occur The oil becomes stringy and sticky and large amounts of fatty acids are formed An intense inflammatory reaction and extreme fibrosis results There is pronounced cellular infiltration of the surrounding lung structures and large multinucleated foreign body giant cells appear Clinically the findings may be those of pneumonia Severity of the lipoid pneumonia is influenced by the quantity of animal oil amount of fatty acid and bacterial infection

Once mineral oil enters the alveoli it is questionable whether it is ever eliminated Since it is an inert material incapable of saponification it resists all efforts of phagocytes to digest it It may be carried with little change via the lym

(4) Am. J Roe tge 1 6 788 797 D ember 1949

phatics to the hilus There is an extreme degree of cellular reaction which results in fibrosis and dense almost acellular scar tissue Phagocytic cells may be destroyed by the indigestible oils which they contain A mass of paraffin oil droplets meshed in heavy scar tissue gives rise to paraffinomas which may attain several centimeters in diameter Paraffinomas usually occur in clusters about large bronchial branches near the root of the lung In frozen sections fat globules stain bright red with sudan III but only mineral oil fails to turn black in osmic acid

Paraffinomas by pressure on larger bronchi may produce partial obstruction resulting in bronchiectatic dilatation may produce local inflammation and erosion or may be the basis for development of bronchogenic carcinoma Unless a number of sections are taken from different areas of a tumor mass cancer may be overlooked because of the similar appearance of paraffinomas and malignant lesions

[This article and the following one provide added indirect evidence of the possibility of various irritating substances being responsible for bronchogenic carcinoma The evidence is not accepted generally without many qualifications indicating the need of better proof The recent report of Wynder and Graham (J A M A 143 379 336 May 27 1950) contains data suggesting that excessive tobacco smoking may be an important factor Watson (New York Med 6 15 June 20 1950) offers statistical evidence indicating an absolute increase of cancer of the lung exceeding considerably the proportion of change in the rate of deaths from cancers in other structures such as the stomach prostate and pancreas He likewise is inclined to implicate heavy smoking as a cause on the basis of an analysis of the habits of patients treated in Memorial Hospital New York City—Ed]

Asbestosis and Cancer of Lung An editor[5] points out that numerous recent reports tend to indicate a causal relationship between asbestosis and cancer of the lung Incidence of cancer of the lung in persons with asbestosis is excessive (as high as 15 per cent in some reports) since the normal death rate from cancer of the lung among adults examined at autopsy is about 1 per cent Moreover there was a distinct shift in sex distribution of lung cancer in a series of asbestosis cancers recently reported from England Male female sex ratio was 2 4 1 whereas it is 5 1 for cancers of the lung in general This shift indicates that an environmental and evidently occu

(5) J A M A 140 1 19 1 0 A g 13 1949

pational carcinogen was active in the asbestosis group tending to equalize the incidence of lung cancer for the sexes Recent experimental observations support this interpretation of clinical evidence

Since some 20 000 workers are employed in the asbestos producing industries of this country and Canada and many additional thousands in various asbestos consuming industries more attention by the medical profession to this probable occupational hazard of cancer of the lung is desirable Cytologic examinations of the bronchial secretion may well be included in periodic examination of workers exposed to asbestos dust whenever clinical or roentgen evidence indicates the possibility of a pulmonary cancer Since available evidence shows that occurrence of cancer of the lung is related to pulmonary asbestosis and is not merely a possible sequela of exposure to asbestos dust autopsy with detailed histologic analysis should be done in all fatal cases of asbestosis The anatomic lesions produced by asbestos dust in the lungs at times make it difficult to distinguish by clinical and roentgen diagnostic methods between pneumoconiotic changes and those that might indicate a cancerous growth

Bronchial Carcinoma Practical Method of Early Diagnosis is described by K K Cross T E Corcoran T J Cooper and S N Landis[6] (Veterans Admin Hosp Des Moines Ia) Bronchial aspirations and washings were embedded sectioned and stained and examined microscopically Such preparations amount to minute biopsy specimens (Figs 47 and 48) and show less distortion than is produced when smears are prepared

METHOD —In all cases in which carcinoma of the lung is suspected bronchial aspirations and/or washings are obtained regardless of other findings or procedures The material is placed in Formalin and subsequently centrifuged at 1 000 2 000 rpm for 10-45 minutes After a minimum of four hours fixation the supernatant is decanted and the remaining button treated as any other surgical specimen If four sections are taken from four different levels of the block the likelihood of finding cancerous tissue will be increased

This method was used in 101 specimens from 81 patients Specimens of 2 were suggestive but not diagnostic of 3 strongly suggestive and of 10 diagnostic of cancer No diagnosis of cancer was reported for nine Of this group of 24 pa

(6) A h P th. 48 491 50 De embe 1949



F g 47 (t p) —S ct on f b on hial w h g f eopl t t × 200
F g 48 (b tom) —B p y p m how g poo ly d ff t d ma
H m t yl d n × 200
(C t y f C os K R t l A h P th 48 491 50 D mbe 1949)

tients carcinoma of the bronchi was subsequently proved at biopsy surgical resection or autopsy or by acceptable clinical criteria

[Th s method deserves further invest gat on in view of the s mplicity which is claimed for it Cytolog c stud es of bronchial d scharge certainly offer p omi e of earlier d agnosis of bronchial ca cinoma —Ed]

Pathology of Subacute Cor Pulmonale in Diffuse Carcinomatosis of Lungs is discussed by A D Morgan[7] (Westminster Hosp London) He describes a case of lymphangitis carcinomatosa of the lungs complicating an undiagnosed gastric carcinoma and giving rise to obliterative endarteritis of the pulmonary vessels with right ventricular hypertrophy

(7) J P th & B t 61 75 84 J ry 1949

Man 58 was hospitalized with cyanosis dyspnea and edema and died four days later At age 31 gastroenterostomy had been per formed for duodenal ulcer Five years before death emphysema was diagnosed roentgenographically At this time he began to have epi gastric pain and during the last three years of his life had much pain and flatulence apparently unrelated to food X ray examination 18 months before death revealed gross emphysema with cor pulmonale A barium meal showed a deformed duodenal cap and pylorospasm suggestive of continued duodenal ulceration

Seven weeks before death another barium meal showed the stoma functioning well after some initial delay but tumor was not sus



F g 49 —Tr e se s ct of h rt sh w g hyp t phy f ght t cul mus le R d d f m × 1 3 (Co t y of M g A D J P th & B t 61 75 84 J n y 1949)

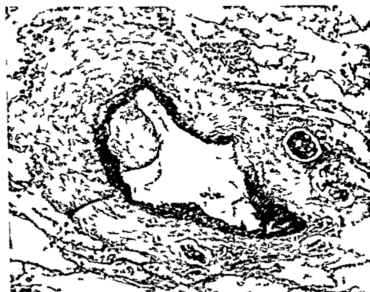
pected A fractional test meal however showed achlorhydria even after histamine One month before admission breathlessness greatly increased and a few days before admission orthopnea and dependent edema developed

He appeared wasted orthopneic and cyanosed with edema of the face elbows hands sacrum and ankles The chest was emphysem atous Auscultation revealed a triple rhythm heard most clearly in the epigastrium The liver margin was tender and palpable 4 in below the costal margin

Postmortem examination of the stomach revealed a sclerosing carcinoma of the leather bottle type The heart weighed 370 Gm

the increase being due entirely to hypertrophy of the right ventricle (Fig 49) Microscopic examination of the lungs revealed two main changes (1) Most of the arterioles were completely occluded by a form of obliterative endarteritis (2) The perivascular and peribronchial lymphatics throughout both lungs were distended by plugs of cancer cell (lymphangitis carcinomatosa) (Fig 50)

Study of the literature on diffuse carcinomatosis of the lungs revealed that in three fourths of the cases the primary tumor was a gastric carcinoma seldom diagnosed during life



Fg 50 —P lm ry l b w g fit p oc g w g f m t ma w th p l fib os d Hem t yl d os R d d f m × 75 (Court y f M g n A D J P th & B t 61 75 84 J y 1949)

Analysis of the histologic reports in 78 published cases showed that there is no clearcut histologic distinction between the group in which spread to the lungs is obviously hematogenous and that in which there is held to be retrograde spread from the hilar lymph nodes (lymphangitis carcinomatosis) One third of the cases of lymphangitis carcinomatosa showed tumor cells in the blood vessels as well as in the perivascular lymphatics frequently associated with diffuse obliterative endarteritis or organized thrombosis

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F g 49 —T a e se sect on f h art sh w g hype t phy f r ght v t cul r mus le Red d f om × 1 3 (C t y of M g A D J P th & B t 61 S 84 Ja y 1949)

pected A fractional test meal however showed achlorhydria even after histamine One month before admission breathlessness greatly increased and a few days before admission orthopnea and dependent edema developed

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All 15 of the patients with adenoma of the bronchus which responded well to endoscopic therapy had the endo bronchial type of tumor Seven were cured and eight became symptom free In all but one of the successfully treated pa tients the tumor was located in the main bronchus or trachea in the one it originated in the right middle lobe bronchus Of patients in whom treatment failed only five had tumors in the main bronchi in the others it was in the lower upper or middle lobe bronchi Thus accessibility of the tumor to bronchoscopic manipulation could be an important factor in determining success or failure In the successfully treated pa tients tumor duration was 3 3 years but for the five main bronchus adenomas not responsive to endoscopic therapy average duration was 21 2 years This long period allows time for extrabronchial extension and favors formation of irrep arable suppurative disease of the lung distal to the tumor conditions requiring surgery for cure Tumors associated with stenosis of the bronchus or having evidence of extrabronchial compression proved not amenable to endoscopic therapy In the successfully treated patients the normal architecture of the bronchus was apparent at the fifth bronchoscopic exami nation

If tumors cannot be eradicated completely and the normal bronchial architecture visualized after a fair trial period sur gery is indicated Recurrent hemoptysis and continued exacer bations of lung suppuration point to the need for surgery Local endobronchial recurrence is evidence of incomplete eradication of a slowly growing tumor and should not suggest malignancy or the need for immediate surgery

[The p ognostic s gnificance of bronchial adenoma is still debated There has been increasing evidence that the tumor may be invasive locally and n rare cases it may give ri e to metastases in the regional lymph odes As a rule it seems best to resect the lobe or segment of lung conta ning the neoplasm —Ed]

Bronchial Adenoma Herman J Moersch and John R Mc Donald[9] (Mayo Clinic) observed bronchial adenoma in 45 men and 41 women aged 15 67 Cough hemoptysis and pain were the symptoms most frequently complained of In 74 per cent roentgen study showed appreciably significant pulmonary changes Of the 84 patients subjected to bronchoscopy the

(9) J A M A 14 99 304 F b 4 1950

Of the 11 cases accompanied by right ventricular hypertrophy 10 showed an obliterative lesion of the pulmonary arterioles in the form of intravascular fibrosis or more recent thrombosis There is thus reason to believe that subacute cor pulmonale is due not to lymphangitis carcinomatosa per se but to occlusion of the pulmonary arterioles The suggestion is made in the light of these findings that lymphangitis carcinomatosa follows a hematogenous spread of tumor cells to the lungs rather than a retrograde spread from the hilar lymphatics

[The conclusion reached by Morgan seems rational and well supported by his evidence Clinically his concept is significant since patients sometimes present symptoms principally of respiratory failure and cor pulmonale which may lead to an erroneous diagnosis of simple fibrosis or some other block between the pulmonary alveoli and capillaries —Ed]

Adenoma of Bronchus Endoscopic Treatment in Selected Cases Max L Som[8] (Mount Sinai Hosp New York City) reviewed 50 endoscopically diagnosed and histologically proved cases of bronchial adenoma This lesion may be distinguished from cylindroma a much more invasive variety of mixed tumor which should not be included in this group by the appearance of cells in solid alveolar arrangement with a delicate stroma and the uniformity in size shape and staining character of the cells

Bronchial adenomas may be divided into endobronchial and intramural or extrabronchial types The endobronchial type has a globular shape which accommodates itself to the lumen of the bronchus It presents a smooth polypoid surface over which the bronchial mucosa is reflected and has a limited attachment to the bronchial wall usually by a pedicle but occasionally is more sessile The other type presents a smooth broad surface endobronchially but extends beyond the boundaries of the bronchus and projects into the peribronchial tissue It replaces bronchial structures and invades adjacent glands In such instances it may cast a dense shadow on the x ray film and occupy a large area of lung parenchyma These tumors probably originate from the bronchial glands or their ducts They are more prevalent among men than women and occur predominantly in the third and fourth decades

(8) J Thorac Surg 18 462-47 August 1949

fibromatosis was present in three of five cases reported in the literature These findings the significance of which is not clear are not of diagnostic aid in differentiating intrathoracic neurofibroma from intrathoracic meningocele but add considerable confusion since mediastinal neurofibroma might be expected as part of a generalized Recklinghausen syndrome



Fg 51—F ontal p j t h w g d m l d d ty pol f l ft th m u g 7 m d m (C t y f By F X t l J Th S g 18 94 303 J 1949)

Aside from thoracotomy or thoracostomy the only procedure useful in differential diagnosis is intraspinal injection of an opaque medium and the positioning of the patient so as to fill if possible the suspected meningocele

The simplest explanation of the production of meningocele would be herniation of the dural envelope of the spinal nerve through the intervertebral foramen with pressure necrosis of the vertebral bodies and enlargement of the foramen as the meningocele enlarges

adenoma was visualized in 78 and biopsy was positive in all but 3 Apparently adenomas originate in the larger bronchi The best explanation for this localization is that they arise from mucous glands which are more numerous in large bronchi than in smaller ones

In this series 10 per cent of the lesions were of cylindroma type and 90 per cent of carcinoid type Grossly all adenomas tend to polypoid projection into the bronchus but frequently most of the tumor is situated in the bronchial wall and in the adjacent pulmonary tissue Sputum examination is of value in differential diagnosis in bronchogenic carcinoma results are usually positive but they are consistently negative in adenoma Cylindroma usually has a wider base of attachment and therefore presents a more difficult therapeutic problem than adenoma of the carcinoid type In five patients there was definitely proved metastasis and in three others there were probable metastases which were not proved microscopically

Of the 36 patients treated bronchoscopically 19 are living 6 have had recurrence with subsequent operation 6 are dead and the follow up is incomplete for 5 Of 51 treated by surgery exploration only was performed in 3 40 are well and 8 are dead Bronchoscopic treatment is recommended for patients with a pedunculated adenoma situated so that it can be removed readily for elderly patients and for those with lesions situated close to the carina so that pneumonectomy would have to be performed After bronchoscopic treatment repeated examinations with the bronchoscope are necessary because of the likelihood of recurrence Surgery is advisable for all other patients and those with evidence of recurrence

Intrathoracic Meningocele Francis X Byron (Los Angeles) Emery E Alling (Battle Creek Mich) and Paul C Samson[1] (Oakland Calif) report three cases of intrathoracic meningocele and emphasize that this lesion must be differentiated from the more frequent intrathoracic neurofibroma With either lesion the chest x ray may disclose a uniformly opaque well defined rounded or lobulated intrathoracic mass (Fig 51) and rib changes intervertebral foraminal enlargement or vertebral body destruction (Fig 52)

Superficial neurofibromas and cafe au lait spots were observed in one patient another had cafe au lait spots Neuro

(1) J Thorac S g 18 294 303 J 1949

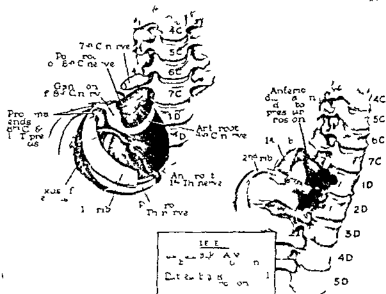
Pulmonary Adenomatosis of Man Review of Literature and Report of Nine Cases Lawrence L Swan (Army Inst of Pathology) proposes that the term pulmonary adenomatosis be reserved for pulmonary tumors which show alveolar cellular proliferation of tall columnar mucus producing type absence of an intrinsic tumor of the bronchial tree and absence of primary adenocarcinoma of any other part of the body Average age in the nine cases reported was 47 2 years there were eight males and one female In eight cases symptoms were of 4 15 months duration and in one there were no symptoms the lesion being discovered by routine chest x ray History of exposure to pulmonary irritants was not significant Signs and symptoms in order of frequency were productive cough fever dyspnea weakness weight loss thoracic pain fatigue cyanosis night sweats pleural effusion and clubbing of the fingers Eight patients have died The survivor who was treated by lobectomy was alive at the time of this report Histologically the cases fulfilled all the criteria for pulmonary adenomatosis Metastases were limited to parenchymal lymphatic channels in one lung and to parenchymal lymphatic channels and hilar lymph nodes in another There was widespread metastasis in only one case Confirmation of metastases was not possible in one case in which pneumonectomy was done but autopsy refused

In the 27 acceptable cases in the literature since 1941 the patients ages varied from 17 to 79 There were 12 males and 15 females Evidence of invasion or metastasis was present in 55 6 per cent These data are to be contrasted with the fact that bronchogenic carcinoma occurs far more frequently in males than in females Furthermore they support the statement that most alveolar cell tumors are malignant

When death has resulted from pulmonary adenomatosis the pleural space is usually partially or completely obliterated by fibrous adhesions The pleural cavity may contain fluid in varying amounts and the lungs are voluminous and tend to retain their contours when the chest is opened The visceral and parietal pleurae may be studded with gray to grayish pink nodules The gross distribution of these tumors may be of miliary nodular type diffuse or a combination of these The

( ) A h P th 47 517 544 J 1949

Once intrathoracic meningocele is diagnosed the question of advisability of operation arises Among the previously re ported cases the two patients on whom excision of the sac was performed died of empyema and meningitis, neither had re ceived chemotherapy In both cases difficulty was encountered in closing the defect In one of the authors cases a satisfac tory closure while difficult was attained It is recommended



F g 5 —D w g d m t t ng el t f m g le to fi st l s d r bs d t l w t k f b a h l pl E te t f b r a l b n d struct on s how t r ght (Co rt y f Byro F \ et l J Tho c S g 18 94 303 J e 1949)

that a generous portion of the neck of the sac be saved so that a plicated closure can be carried out A second patient died of shock probably the result of bleeding encountered dur ing surgery In the third patient operation revealed a menin gocele in the apex of the right chest but it was not treated because it was asymptomatic and in a protected place If the sacs are relatively small operation is probably not justified unless serial chest x rays reveal progressive enlargement to the point of progressive respiratory embarrassment

Pulmonary Manifestations of Scleroderma Anatomic Physiologic Correlation David M Spain and Albert G Thomas[3] (Columbia Univ) report a case of scleroderma in which the clinical features were almost entirely related to pulmonary changes

Man 65 had had shortness of breath for 10 years It became progressively worse and was accompanied by ankle edema He was told he had heart disease and was treated unsuccessfully with large doses of digitalis for several years About four years before admission a cough productive of a variable amount of sputum was noted Since that time he had noted changes in the skin and joints Dyspnea cough expectoration and weakness had become progressively severe

In the hospital skin biopsy led to a diagnosis of scleroderma The vital capacity was 1 750 cc and residual air 921 cc compared with normal values of 4 140 and 1 335 cc respectively Arterial oxygen saturation at rest was 91 1 per cent and after exercise 81 per cent The right ventricular blood pressure was 71/3 mm Hg compared with a normal of 28/0 4 The arterial blood pressure was 118/67 mm Hg During the hospital stay weakness increased and dyspnea became so severe that continuous administration of oxygen was required He died 108 days after admission

At autopsy the right lung weighed 900 Gm and the left lung 770 Gm In both the pleura was diffusely granular thickened and opaque The upper lobes of both lungs and the middle lobe of the right were almost completely consolidated and airless On the cut surface there were many thin walled cystlike spaces ranging in size from 2 mm to 1 cm Microscopic examination of lung sections (Fig 53) revealed many varying sized cystic spaces often lined by cuboid epithelium Alveolar septa were diffusely thickened with fibrous tissue and in places infiltrated by inflammatory cells Bronchioles were dilated and in many of the smaller ones the muscular coat was partially replaced by fibrous tissue Pulmonary arterioles had thick wall and narrow lumens

In scleroderma involvement of skin diaphragm fibrous retraction of the pleura and diffuse peribronchiolar fibrosis interfere with the function of getting air in and out of the lungs The most striking changes in the case reported were related to impairment of the respiratory function by pro

(3) A I t M d 32 15 161 J y 1950

histologic picture is essentially the same in the two forms Variations in pattern may range from simple investment of alveoli by a single layer of cuboidal or cylindric cells to complicated arrangements resulting from extensive intra alveolar proliferation of the cells with rupture of alveolar walls and coalescence of spaces

The appearance of the lesions of pulmonary adenomatosis or alveolar cell tumor of the human lung are similar to those in jagziekte a disease of the lungs of sheep and lesions in horses mules guinea pigs and cats It is possible that an identical pulmonary reaction takes place in these widely different species A review of the causes of adenomatosis in these species may shed light on the condition in man As yet no etiologic factor has proved to be specific for the condition in man but the disease apparently is not infectious

Origin of the epithelium like tumors in adenomatosis is undetermined The recent literature has shown a significant trend toward acceptance of the theory of an alveolar epithelial origin Swan supports the view that it is an extrabronchial neoplasm with cancerous potentialities since though it may appear histologically benign it may kill by local growth or by metastases

[The important practical implication of this report is that the diseased lobe or lung should be resected if the adenomatosis is o localized and a proper diagnosis can be made Diagnosis is difficult and in the presence of such chronic diffuse lesions direct biopsy of the lung may be necessary —Ed]

ciated cardiac changes of pericardial fibrosis focal myo cardial fibrosis with thickening of the myocardial arterioles subendocardial fibrosis and hypertrophy with dilatation of the right ventricular myocardium combined to produce myocar dial anoxia and pulmonary hypertension

Essential Brown Induration of Lungs (Idiopathic Pulmo nary Hemosiderosis) N G B McLetchie and Grant Colpitts[4] (Regina Sask) state that this condition is not familial but has been encountered in children aged a few months to 16 years It is characterized by periodic attacks of tachycardia pyrexia pallor fatigue cyanosis increasing dyspnea signs of congestive cardiac failure severe anemia and hemoptysis Lung findings are usually more conspicuous by x ray than clinically and consist of a diffuse bilateral infiltration of coarse mottling against a general background of increased density Between attacks the subject may remain well but usually there is chronic ill health The condition ends fatally

At autopsy the only conspicuous abnormality is in the lungs The lungs are uniformly consolidated and have a firm rubbery consistency the cut surface is a uniform brown red without evidence of inflammatory processes A copious blood stained frothy fluid may be extruded from the cut surface on pressure Microscopically there are alveolar thickening due to capillary dilatation thickening of capillary and alveolar basement membranes generalized interstitial edema and gen eralized increase of reticulin and collagenous fibrils The elastica in the lung is grossly deficient and almost completely absent in the alveolar walls and septa The lung consolidation is due to filling of the alveoli with red blood cells and macro phages laden with hemosiderin Almost all the changes can be considered secondary to anoxemia

Although the essential nature of the disease is unknown lung inelasticity due to hypoplasia of the elastica or a vaso motor abnormality of the lesser circulation may be of pri mary importance

Hemosiderosis of Lung Due to Mitral Disease Report of Six Cases Simulating Pneumoconiosis According to Eugene P Pendergrass Edwin L Lame and Herman W Ostrum[5] (Univ of Pennsylvania) mitral valve disease may be accom

(4) C ad M A J 61 1 9 133 A gu t 1949
(5) Am J Roe tg l 61 443 456 Ap 1 1949



F g 53—Photom crog aph of l g H mato yl n nd e ×20 (C t y of Spa D M. d Th ma A G A n Int. Med. 3 152 161 J n ary 1950)

nounced thickening of alveolar walls narrowing of arterioles and thickening of their walls These changes interfered with exchange of gas over the alveolar interface as illustrated by a low oxygen content of arterial blood after exercise Asso



Fg 56 (t 1—H op thol g c 1 t 1 f l g f s m t t t sh g 1 fibros 1 eg 1 lump f m oph g nt m g h mo d e n m tly t al eo' Thick ed septa nd se e h o pas e co g st n Redu d f or × 35
Fg 57 (bottom l ft)—R d ed 1 om × 400
Fg 58 (bott m ght)—R d d f m × 950
(Cou t y f P d g s L P et al Am J Roentge 1 61 443 4 6 Ap 1 1949)

from numerous others that may produce a finely nodular x ray density in the chest Helpful confirmatory evidence is a mitral configuration of the heart and a history of rheumatic valvular disease

panied by deposition of hemosiderin in the lungs so that x rays reveal a fine nodulation (Figs 54 and 55) resembling pneumoconiosis or miliary tuberculosis This condition is rare only 17 cases studied at autopsy being collected from the world literature In the series reported four cases were studied at autopsy two patients are still living

Of the four cases studied at autopsy all showed chronic passive congestion some of which was severe In two there was hemosiderosis and in the others siderofibrosis All the



F g 54 (l ft) —X ays f pat ent dy ng f h umatic m t al heart d se se aut p y d g o wa p lm a d ofib
F g 55 (ght) —Nod le oentg g m m a u up to 3 mm i d met r (Co rt y of P g k l t al Am J Roentgen l 61 443 456 Ap l 1949)

microscopic sections contained nodular aggregates that could be identified grossly as areas of hemosiderin deposition (Figs 56 58) By the Prussian blue test diagnosis was confirmed The aggregates of iron pigment varied from 1 to 3 mm in diameter Their size distribution and shape govern the degree of x ray visualization

As evidenced by the diagnosis in two living patients this condition occurs in those with mitral valve disease living comfortably without clinical evidence of lung congestion It is conjectured that these persons have hemosiderosis with inactive chronic passive congestion

For diagnostic purposes the lesion must be differentiated

aid of antibiotic drugs seven patients are still alive The survivors ages range from 2 to 14½ years

Chest x rays may disclose extensive pulmonary changes which can be divided into two stages In the first there is evidence of bronchial plugging without much infection and the picture of obstructive emphysema with poor air exchange may be recognized The second stage shows infection with



Fig 60—Secton f b on h f m l ft l q b w g m ta[l f ep th l m. (C rte y f D key L B D f Ch t 17 151 156 F bru ry 19 0)

increased hilar shadows and prominence of vascular markings Bronchiectasis is usually present but use of lipiodol* is not warranted for confirmation In long standing pulmonary disease the apexes and bases are equally involved but there is no evidence of pleural reaction Irregularly emphysematous lungs prominent hilar shadows and bronchovascular markings extensive peribronchial pneumonia areas of atelectasis bronchiectasis and bronchiectatic abscesses may be noted but are not specific though they should suggest the diagnosis

Pulmonary Disease, Associated with Cystic Fibrosis of Pancreas is discussed by Lloyd B Dickey[6] (Stanford Univ) who reports experience with 10 patients In any child with a chronic respiratory infection especially if it extends from the tip of the nose to the alveoli with sputum and negative tuberculin this disease should be suspected at once Sex distribution was about equal four had symptoms from birth whereas two did not have symptoms until age 14 months The initial symptom in five was cough and in five it was the character of the stool Cough and respiratory symptoms developed in the latter group in 14 months to 5 years A history of a sibling dying previously with a clinically similar disease was found in three cases Typical stools with increased fat content were noted in seven When the tests were carried out four showed no trypsin activity in the duodenal contents and four showed minimal activity



Fg 59—C t s fa of l ft lung of fant wh d d t g 7 m th show g cb s p p r t b h t b on h ect pper lob nd p d enl g m t of pe b ch l d (Co t y of D key L B D f Chest 17 151 156 F b y 1950)

There was decided evidence of paranasal sinusitis in four three had pronounced heavy chronic nasal discharge and two had postnasal pus Otitis media occurred in three including one without evidence of sinusitis The sputum of seven contained Staphylococcus aureus coagulase positive and in one hemolytic streptococci were found but in two bronchial secretions contained no pathogenic organisms Physical examination disclosed malnutrition in all but one and chest involvement in all x ray studies showed pronounced lung involvement in all but one Death occurred in one patient at age 7 months and in another at age 27 months Both showed fibrocystic disease of the pancreas and extensive pulmonary disease (Figs 59 and 60) consisting of bronchitis pulmonary abscess bronchiectasis and bronchopneumonia With the

(6) D of Ch t 17 151 156 F brua y 1950

generalized disease of unknown etiology occurring in an acute or chronic form In the acute variety which occurs in infancy and early childhood there is progressive infiltration of the skin bone lymph nodes and viscera leading to early death The chronic variety occurring in older patients may be present in the complete form with pituitary bone and lung dis



F g 61 (l ft) —Cy t f t ght f m r below ol j f ctu
F g 62 (ght) —C l d t cul t on bo h l gs.
(C t y f F k so T B t M J 1 10 9 1030 J 11 1949)

ease or in the incomplete form in which one or a combination of these systems is involved In the chronic form lung fibrosis and cyst formation may be the sole manifestations or there may be association of pituitary disorders with honeycomb lungs

Radiologic Morphology of Fatty Embolism of Lung was followed serially by Georges Voluter[8] (Univ of Geneva) The patient was a man aged 25 who had a comminuted fracture of the left femur and died *three days after onset of coma*

(8) A ta d 1 31 403 430 1949

Early and vigorous treatment should be instituted for the pancreatic deficiency and should include large amounts of vitamin A If pulmonary symptoms are striking oxygen should be administered and tenacious mucus secretions re moved by mechanical suction Penicillin aerosol should be in stituted but in small infants the intramuscular route may be used If penicillin resistant organisms appear streptomycin or aureomycin may be useful Adequate dosage should be con *tinued until the respiratory tract is clear of disease and to* some extent prophylactically during remission Local treat ment sometimes surgery may be needed for sinusitis Avoid ance of exposure to infection should be rigid at all times and all prophylactic measures must be used against such diseases as measles and pertussis

Eosinophilic Xanthomatous Granuloma with Honeycomb Lungs Thomas Parkinson[7] (St Bartholomew s Hosp Lon *don) points out that eosinophilic granuloma Hand Schuller* Christian disease and Letterer Siwe disease are but phases of the same disorder and to avoid confusion recommends that the terminology of Thannhauser eosinophilic xanthomatous granuloma be used He reports the following case

Man 56 was hospitalized in September 1948 complaining of increasing dyspnea on exertion during the preceding six years Be cause of the x ray finding of diffuse pulmonary shadows at the time of onset of symptoms he had been treated in a sanatorium In 1944 the right femur had been fractured X rays showed a cyst at the fracture site The fracture healed well in four months but nine months before admission pain recurred at this site There was onset of polydipsia and polyuria seven months before admission which could be partially controlled by a proprietary pituitary snuff Physical examination disclosed a few rhonchi and some thickening of the right femur over the site of the old fracture An x ray of the femur (Fig 61) showed a cystic area and there was general ized reticulation associated with miliary mottling of both lung fields in the chest x ray (Fig 62) Tomography confirmed the presence of small cystic areas *in the lung A biopsy of the right femoral* cyst was thought typical of eosinophilic granuloma of bone Dia betes insipidus was controlled by pitressin® tannate and pain in the leg was completely relieved by a course of deep x ray therapy to the femur Deep x ray therapy to the pituitary fossa and lungs did not change the appearance of the chest x ray or improve the symp toms

Parkinson suggests that this condition be regarded as a

(7) Brit M J 1 10 9 1030 J 11 1949

generalized disease of unknown etiology occurring in an acute or chronic form In the acute variety which occurs in infancy and early childhood there is progressive infiltration of the skin bone lymph nodes and viscera leading to early death The chronic variety occurring in older patients may be present in the complete form with pituitary bone and lung dis



F g 61 (l ft) —Cyst r f t ght f m b low 11 f t
F g 6 (ght) —(l d t l t both l g
(C t y of P k Γ B t M J 1 10 9 1030 J 11 1949)

ease or in the incomplete form in which one or a combination of these systems is involved In the chronic form lung fibrosis and cyst formation may be the sole manifestations or there may be association of pituitary disorders with honeycomb lungs

Radiologic Morphology of Fatty Embolism of Lung was followed serially by Georges Voluter[8] (Univ of Geneva) The patient was a man aged 25 who had a comminuted fracture of the left femur and died three days after onset of coma

(8) A ta d l 31 403 430 1949



Fig 63 —L ft uppe d m ddl p hil r Note d l tatio of left en t le Se ond pb e (24 hou ft o t f c m) f f tty e b l m f l i g The e alm t e lus v ly at l t t e ud t a pe t (w t lor p t x) Ph e of nflu nce f c nar exud t and t st t l fo ı Fo th h st t m th b a t shadow s t sed p pally t the ght (Cou t y f Vol t G A ta ad ol 31 403 430 1949)

The three following morphologic phases were distinguished

1 A roentgenogram made 26 minutes after onset of coma showed an agglomerated miliary stage of two types images due to fatty and medullary filling of vessels of the pulmonary circulation and embolic elements (follicular stellate foci) in the general circulation The heart shadow was unchanged

2 In a roentgenogram made 24 hours after onset of coma the large agglomerated foci had disappeared and there was confluence of acinar and interstitial foci in both circulations The heart shadow was increased for the first time—more on the left than on the right—and the amplitude of contractions was decidedly decreased The homogeneous shadows (milky aspects) in the peripheral parenchyma hilar region and even in the hilar projection itself must be due to atelectatic exudative phenomena caused by circulatory disturbances (edema) and by aeration disturbances (Fig 63) Because of its morphologic elements this phase could be called the atelectatic exudative and miliary stage

3 Three days after onset of coma there was a purely granular stage which was hard to demonstrate There was an astonishing rarefaction of the pathologic picture but examination under magnification revealed over the entire pulmonary area a crop of small stellate foci with extremely low radioabsorption The small size of the heart was striking

The physician must be alert and must use all available precision methods to discover the slightest trace of a miliary constellation which although only visible in the upper and subparietal areas may give a clue to an intense process disseminated over the entire pulmonary surface

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DISEASES OF THE PLEURA

Defensive Mechanisms in Mediastinum, with Special Reference to Mechanics of Pleural Absorption were investigated by G H Cooray[8] (Univ College Hosp Med School London) Particulate matter introduced into the pleural cavity of animals was found to pass through definite zones in the me

(8) J P th & B ct 61 551 567 O t b 1949

diastinal pleura These points of exit known as Kampmeier s foci are guarded by collections of macrophages which lie im mediately below the pleural mesothelium (Fig 64) The phagocytes form an efficient protective mechanism because they ingest India ink bacteria red blood cells oil globules silica and colloidal dyes such as trypan blue very quickly Although the pleura actively participates in absorption these barriers prevent dissemination of irritants in the mediastinum



F g 64—Inj t l p e d f t o d c pleu sh w g s l K mpm foc w th v l tw k H h m t yl d d f m × 60 (C l f Coo y G H J Path & B t 61 551 567 O t b 1949)

and by the blood stream Clinical experience with mediastinitis supports these observations Structures morphologically iden tical with Kampmeier s foci in animals have been demon strated in human mediastinal pleura The presence of these structures may partly explain why the mediastinum is so re sistant to infection from the pleural cavity

Activity of Kampmeier s foci is intimately connected with the direction of movement of intrapleural fluids which in turn depends on respiratory movements The motive force is pro vided mainly by contractions of the diaphragm During dia phragmatic descent on inspiration strong suction causes the intrapleural contents to be drawn toward the diaphragm from

the potential space between lung and chest wall Expiration is not sufficient to drive fluid back to its original position It escapes into the region between the lungs and the retrocardiac mediastinal pleura where there are collections of phagocytic cells Diaphragmatic paralysis abolishes movement toward the absorptive zones and particulate matter remains in the pleural cavity

Absorption is preceded by attachment of particles to the mesothelium over the Kampmeier s foci Penetration of particles occurs only in these foci which serve as natural pathways and as a means of exit for pleural fluids In passage through the pleura particles pass both between the mesothelial cells and through their living cytoplasm Transmission is effected by respiration in the early stages and by carriage within phagocytes in the later stages of absorption The mesothelium lining Kampmeier s foci is distinctly different from the rest of the pleural mesothelium The cells are of smaller size and there is a consequent increase in the total amount of intercellular space Mucin occurs in these cells and probably assists in the attachment of particles to the phagocytic systems When trapped in this manner bacteria are more easily attacked by the macrophages

Reactions of the foci after entry of particles depend on their nature but the end result—localization of the irritant and prevention of its spread—is similar in all instances The macrophages proliferate after phagocytic activity and coalescence of adjacent foci results India ink is ultimately completely encapsulated by mature fibrous tissue Bacterial suspensions incite violent inflammatory reactions and polymorphonuclear exudate but the final result is similar Intrapleural injection of red cell suspensions is followed by formation of hemosiderin exclusively within the ingesting phagocytes in these foci Absence of free particles in the mediastinal tissues is demonstrable evidence of the efficiency with which these foci act as barriers in the pleura Intensity of phagocytosis is enhanced by deep breathing or dyspnea

In experimental mediastinitis it was observed that India ink or bacterial particles introduced directly into the mediastinum follow a characteristic course moving away from the midline toward the pleura This movement serves as a safety device causing irritants to leave vital thoracic structures so

that they can be efficiently dealt with by phagocytes of the Kampmeier s foci There is also a caudal spread toward the base of the mediastinum where irritants reach the retrocardiac pleura with consequent exposure to foci in this location These two modes of spread are mainly instrumental in preventing gross damage to the lungs and pleura Formation of localized abscesses is another protective device which prevents dissemination in mediastinal tissues Kampmeier s foci because of their strategic position in the mediastinum act as barriers to the spread of infection either to the pleural cavity or from the mediastinal tissues They constitute the mediastinum s first line of defense

[This is an unusually informative study The infrequency of mediastinal invasion by bacteria and other particulate matter from the pleura always impresses the clinician but the mechanisms of defense have been poorly understood

It is necessary to distinguish between mediastinitis and mediastinal pleurisy clinically The latter occurs relatively often and represents inflammation of the pleura covering the mediastinal space the tissues within the space seldom participate in the inflammation —Ed]

Pleural Shock Andrew Morland[9] (Univ College Hosp London) reports five cases of serious accidents in paracentesis of which one was fatal These cases represent an incidence of about 1 in 10 000 *punctures of the pleura* All occurred during aspiration of fluid a procedure invariably preceded by local anesthesia There was some degree of infection in all *and in one case there was irritation of the pleura* Air embolism can probably be excluded in all cases The evidence suggests that disturbance of the heart from reduction of *intrathoracic pressure is the most likely cause of the* sudden loss of consciousness Such accidents are more likely to happen when the pleura is thickened and inelastic and it is therefore *important to avoid very low pressures during aspiration* or replacement of fluid

Air embolism is the most likely explanation of the rare *serious or fatal accident during* pleural puncture Sudden death without signs or symptoms of cerebral embolism does not necessarily mean shock since with a patient in the horizontal *position air may* occlude the coronary vessels Passage of air through the chest wall is not essential for production of air embolism for as in the cases described by Morland it may *occur during* aspiration of fluid

(9) Lancet 2 10 1 1023 Dec 3 1949

When lung tissue is indurated by chronic inflammation the veins are held open and cannot contract when mechanically injured The needle may make a communication between airway and vein and deep respiration may suck sufficient air into the vessel to cause embolism Other causes of syncope during paracentesis include status lymphaticus and the psychic effect of needle puncture

Mechanism of Pleural and Ascitic Effusions with Suggested Method for Indirect Estimation of Portal Venous Pressure, is discussed by A H James[1] (St Mary s Hosp London) Antecubital venous pressure and effusion fluid pressure were measured simultaneously in 17 patients with pleural effusions and in 24 with ascites Congestive failure constric

MEAN FLUID PROTEIN LEVEL (GM /100 ML.) IN DIFFERENT DISEASES

	P u		A ti	
	Album	Gl b l	Alb m	Gl b l
Heart failure	1 3	0 8	1 8	1 3
Constrictive pericarditis	1 9	1.2	2.2	2 3
Carcinoma	2 9	1 3	2 4	1 2
Tuberculosis	3 1	2 2	3 1	2 1
Nephrosis		..	0	0.2
Cirrhosis	..	...	0 5	0 7

tive pericarditis carcinomatosis tuberculosis and cirrhosis were the commonest causes of effusions The albumin and globulin content of plasma and of effusion fluid were determined *in each patient and the colloid osmotic pressures* calculated (table)

Venous pressure always exceeded pleural pressure in patients with pleural effusions The difference between the two was approximately equal to the difference between the colloid osmotic pressures of plasma and fluid Venous pressure exceeded ascitic pressure in most of the patients with ascites due to causes other than cirrhosis The difference between the two was proportional to the difference between the colloid osmotic pressures of plasma and fluid This proportionality was not observed in patients with ascites due to cirrhosis In seven of nine of these patients ascitic pressure exceeded venous pressure and the difference between the colloid osmotic pressures was large owing to the low protein content of ascitic fluid It is suggested that portal obstruction accounts for the

(1) Cl S 8 291 314 D mbe 1949

different behavior of ascites due to cirrhosis and that the magnitude of the deviation provides a measure of the portal pressure If cirrhosis of the liver is excluded because in this condition portal obstruction intervenes the findings are in general agreement with Starling s theory that a proportionality exists between the colloid osmotic and hydrostatic forces

The albumin content of effusion fluid was proportional to that of plasma but the globulin contents were not related except in tuberculous pleurisy Effusion fluids caused by tuberculosis or carcinoma contained more protein than those caused by congestive failure The correlation of plasma and effusion fluid albumin levels is most easily explained by assuming that some of the capillaries in contact with the effusion are permeable to albumin so that it enters effusion fluid largely by simple diffusion Globulin probably only enters effusions when capillary permeability is markedly increased by inflammation The general supposition that inflammatory diseases cause effusion of fluid with large amounts of protein in contrast to congestive failure cirrhosis and nephrosis is confirmed

Hypoproteinemia is usually found in patients with effusions being more severe in those with ascites particularly if caused by cirrhosis

Pulsus Paradoxus and Pleurisy W Eric Gibb reports two cases in which pulsus paradoxus occurred in association with massive pleural effusion It is well known that idiopathic pericarditis and pleurisy may coexist and that when of tuberculous etiology either may be fibrinous or exudative But it is also well to recognize that pulsus paradoxus can occur in the presence of a large pleural effusion alone and therefore such inspiratory waning of the pulse does not necessarily indicate pericardial effusion Whereas a pericardial effusion which gives rise to pulsus paradoxus should give other signs of its presence but frequently results only in moderate dyspnea a pleural effusion of sufficient size to give rise to pulsus paradoxus is also accompanied by marked dyspnea and distress Pulsus paradoxus in a case of pleural effusion is an indication for removal of 20 30 oz fluid immediately

Pulsus paradoxus in pericardial effusion and mediastinopericarditis is coincident with severe interference with venous

( ) B t J T b 43 1 6 J a y 1949

filling of the right side of the heart whereas its presence in deep inspiratory breathing in normal subjects is associated with pooling of blood within the pulmonary circulation and therefore a lessened venous return to the left side of the heart In gross intrathoracic disease including massive effusions and after pneumonectomy blood flow to the left auricle is likewise decreased and therefore output from the left side of the heart lessened

Study of Coagulation Mechanism of Pleural Blood in Hemopneumothorax is presented by Stuart W Cosgriff[3] (Columbia Univ) In a patient with hemopneumothorax the pleural blood failed to clot on removal from the chest but its hemoglobin content hematocrit and plasma specific gravity were comparable to that of circulating intravascular blood The essential constituents for coagulation prothrombin thrombin and fibrinogen were completely absent from the pleural blood specimen Calcium was present in normal amounts When the hemothorax plasma was recalcified for prothrombin determination it failed to clot It was impossible to demonstrate any form of anticoagulant activity in the pleural blood though incoagulability was confirmed on several occasions

Since the essential factors for coagulation were absent it was concluded that coagulation had occurred before thoracentesis Apparently coagulation of blood proceeds within the pleural cavity in the usual fashion and the so called incoagulable hemothorax fluid was really serum in which some of the formed elements of the blood were suspended

[The accumulation and defibrination of extravasated blood in the pleura has been observed frequently in clinical practice The fibrin sometimes forms into a ball particularly in the presence of pneumothorax and this may move about in the pleural space after serum has been absorbed Eventually the fibrin ball becomes fixed and is absorbed or organized —Ed]

Relation of Idiopathic Pleurisy and Pleural Effusion to Tuberculosis K S Maclean[4] (Cambridge Univ) noted that in 17 of 107 Royal Navy personnel with pleural effusion but in only 2 of 120 with dry pleurisy tuberculosis subsequently developed The difference in subsequent incidence of tuberculosis in the two groups is highly significant and indicates that

(3) Am J Med 8 57 61 J y 1950
(4) G y H p R p 97 133 184 1948

tuberculosis is much more likely to follow pleural effusion than idiopathic dry pleurisy

Upper respiratory infection was twice as common before dry pleurisy as before effusion Fever disappeared in less than three weeks in 87 3 per cent of patients with dry pleurisy but persisted longer in 79 2 per cent of those with effusion Fluid was present more than six weeks in 87 4 per cent of those with effusion whereas in 89 7 per cent of those with dry pleurisy friction rub disappeared in less than six weeks Sedimentation rate was more likely to be elevated in patients with effusion but leukocytosis was rare in both conditions From x ray evidence it is apparent that dry pleurisy has much in common with bronchitis or bronchopneumonia and occurs more frequently in the higher age groups than does pleural effusion

Tuberculosis is more likely to follow when the effusion is large its duration long and fever sustained and is even more likely when the patient is between 20 and 30 The commonest tuberculous complication of effusion is an infiltrative lesion at the common situation for postprimary tuberculosis the subapical areas of the upper lobes Results agree with the accepted view that the likelihood of sequelae decreases with time

In differential diagnosis of pleural effusion transudates may be distinguished from exudates in that the former have a specific gravity under 10 15 a low protein content and no clot formation They are frequently associated with cardiac or renal disease Effusions secondary to malignant disease or pyogenic lung infections are often difficult to differentiate from those due to tuberculosis Malignancy is the commonest *cause of effusion in patients over 40 and may be differentiated* by thoracoscopy pleural biopsy x ray examination of the lung fields after removal of fluid by aspiration or detection of malignant cells in the pleural fluid or sputum Aid in diagnosis of pneumo or streptococcic effusion may be derived from the rapid response of fever to chemotherapy high leukocyte count elevated respiratory rate in the absence of severe pleuritic pain absorption of effusion within three to four weeks and the finding of a predominately polymorphonuclear fluid A history of a pleuritic incident within the previous six months is strong evidence that tuberculosis is the re ponsible agent Patients in whom a pleural friction rub of dry pleurisy

persists for more than two or three weeks are more likely to develop tuberculosis than those in whom signs and symptoms clear rapidly In general every case of idiopathic pleural effusion must be considered tuberculous until proved otherwise but the converse is true for dry pleurisy

Direct inhalation into the lungs must be the usual route of infection in pulmonary tuberculosis For production of tuberculous effusion tubercle bacilli or tuberculoprotein must come into contact with a hypersensitive pleural membrane The latter appears to develop some months after the primary complex Such an effusion almost always occurs on the same side as the complex but the exact route by which the bacilli reach the pleural membrane after primary infection has not been settled Should organisms come into contact with a non hypersensitive pleura dry pleurisy may result Once the pleura has developed hypersensitivity effusion may occur at any stage of the disease

Tuberculous pleural effusion commonly follows Mantoux *conversion when this occurs after adolescence* but is extremely rare before age 15 although most persons have become Mantoux positive at this age The explanation for this may lie in the fact that the initial tuberculous infection is greater after adolescence because at that age larger droplets containing a greater number of bacilli are able to pass the lung defenses and reach the terminal bronchi It is postulated that size of the droplets which reach the terminal bronchioles in children is very much smaller than in adults possibly because of the more efficient working of the ciliated epithelium and consequently the number of virulent organisms is correspondingly less Since adults tend to receive a larger initial dose of infection the primary complex remains active longer and hypersensitivity develops while the pleura is still subjected to the action of tubercle bacilli with the result that fluid is produced

Pleural fluid complicates obvious pulmonary tuberculosis much less commonly than might be expected and is probably due to formation of tubercles on the pleural membrane or rupture of a small tuberculous cavity into the pleural space This relative rarity is probably due to the tendency for bacilli to remain localized to the lesion and to obliteration of the pleural space in the vicinity of the lesion The infrequent association

of miliary tuberculosis with effusion may be due to the rapid ity with which the infection spreads allowing little time for hypersensitivity to develop

Reinfection following tuberculous effusion is by an endog enous source such as the initial focus the obliterated basal pleural space and adjacent subpleural areas of the lower lobes In these situations fibrous reaction and concentration of tubercle bacilli is greatest

Infrapulmonary Pleural Effusion Simulating Elevation of Diaphragm Emil Rothstein and Francis B Landis[5] (Veter ans Admin Hosp Wood Wis) observed 12 ca es of this condition 6 in association with pulmonary tuberculosis 1 with bronchogenic carcinoma 1 with heart disease 1 with postpneumonic empyema 1 with metastatic hypernephroma and 2 of unknown etiology Because of the concave shape of the lung base the fluid assumes a convexity superiorly which resembles an elevated diaphragm in the standard postero anterior x ray The convex upper border of infrapulmonary effusions has never been adequately explained but it may be due to fortuitously situated pleural adhesions or encapsulation of the fluid In some of the present cases encapsulation was pro ed by failure of the fluid to shift with changes of position but in nine patients the fluid shifted and in several lateral de cubitus films revealed a free pleural space Factors altering lung retractility may be important in localizing the fluid but in five patients the lower lung was normal by x ray The basic cause of thi configuration is obscure

Diagnosis of infrapulmonary effusion may be aided by careful study of consecutive x rays which reveal the sudden appearance of unexplained elevation of the diaphragm in a patient whose earlier films had no such change Development of minimal blunting of the costophrenic angle is an additional help in diagnosis When the left side of the chest is involved the stomach or colon may contain gas and by their position give a clue to the true level of the diaphragm As a diagnostic procedure 2 drachms citrocarbonate may be used to outline the stomach

Fluoroscopic examination may reveal the exact nature of the condition Diaphragmatic motion is usually well trans mitted to the overlying fluid and its presence may rule out

(5) Am J M d 8 46 52 Jan ry 1950

phrenic paralysis and subphrenic abscess In most cases a definite shift of the fluid is noted in different postures In the supine position the two leaves of the diaphragm become equal and the involved side diffusely more opaque than previously owing to a shift of the fluid along the posterior chest wall X ray studies should be made in the dorsal recumbent and lateral decubitus positions Pneumoperitoneum may be helpful in revealing the true position of the diaphragm particularly on the right side Thoracentesis provides positive proof of an effusion but may be unsuccessful if the fluid is pocketed or so deeply situated as to be inaccessible

Differential diagnosis includes elevation of the diaphragm from various causes subphrenic abscesses hepatomegaly *diaphragmatic hernia lung tumors intrathoracic cysts* and atelectasis

Empyema as Complication of Chronic Pulmonary Tuberculosis In 1 874 consecutive autopsies of chronic pulmonary tuberculosis reviewed by Oscar Auerbach[6] (Halloran Veterans Admin Hosp Staten Island N Y) there were 311 cases of empyema an incidence of 16 per cent In the vast majority the empyema cavity was located in the lateral aspect of the chest It usually extended from the inferior aspect of the upper to the base of the lower lobe In all regions the boundary of the empyema cavity was the fused visceral and parietal layers of the pleura

Artificial pneumothorax was present in 252 (81 per cent) of the 311 cases of empyema whereas in 59 (19 per cent) there was no such antecedent treatment This substantiates the general opinion that empyema is chiefly a complication of artificial pneumothorax Bronchopleural fistulas were present in 153 cases (49 1 per cent) In many other cases of empyema there was a definite episode which pointed to the presence of a fistula during the patient s life These episodes included marked shifts of the mediastinum to the opposite side rapid appearance of highly positive pleural pressures on the affected side expectoration of methylene blue instilled into the pleural cavity and shortness of breath and pain on the side of involvement Auerbach believes that the cause of the empyema in each instance was a bronchopleural fistula although in many the fistulas were healed at the time of autopsy

(6) Am. R T bc c. 59 601 618 T 1949

There was no evidence at autopsy of rupture of an adhesion band in artificial pneumothorax (due to stretching) with subsequent development of empyema In no case could it be proved that the pleural space had become infected from without Evolution of a clear serous effusion into an empyema almost always results from bronchopleural fistula not discovered clinically

In 180 cases (72 per cent) artificial pneumothorax was begun within the first seven months of onset of the disease Empyema is generally an early complication of this therapy but may appear at any time as long as the collapse is maintained in the presence of an open cavity In none of the cases in the present series was there evidence of rupture of an empyema into the lung parenchyma Empyema necessitatis was a complication in 32 cases (9 7 per cent) In all but four it was associated with artificial pneumothorax

THE BLOOD *and* BLOOD-FORMING ORGANS

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PART III

THE BLOOD AND BLOOD-FORMING ORGANS

ADVANCES IN KNOWLEDGE CONCERNING DISEASES OF THE BLOOD 1940-50

During the past decade many new observations and some concepts concerning diseases of the blood and blood forming or gans were doubtless influenced by the war For example the practical need for large amounts of blood and blood substitutes for the armed forces led to the development of blood banks the fractionation of plasma with its various useful by products and studies of the survival of red cells in health and disease Renewal of interest in the chemotherapy of leukemias and lymphomas is also an offshoot of research in the leukopenic effect of toxic war gases These illustrate the hastened fruition of prewar inquiries the roots of which lay just beneath the surface The majority have been covered in the YEAR BOOKS of the decade How much the disturbance of the soil nourishing the deep lying seeds of the significant research of the future may have cost the world we shall never know but may gravely suspect

GENERAL PHYSIOLOGY

In the work of Moore and his associates is found experi mental confirmation in man of the physiologist s belief in the basic control of erythropoiesis by the oxygen content of the ar terial blood Breathing of high concentrations of oxygen had de pressant effects on reticulocyte hemoglobin and red cell produc tion in various types of hemolytic anemias Return to breathing of room air at once resulted in increased bone marrow activity From the work of Young and his colleagues who used the me chanical fragility method of Shen in studies of the survival of dog red cells tagged with radioactive iron it would appear that mechanical destruction in the moving circulation is the factor

limiting the life of successive generations of normal red cells This has been determined at from 100 to 120 days by improved methods of estimating survival differential agglutination of compatible but heterologous transfused red cells tagging with radioactive iron or persistence of circulating hemoglobin containing heavy nitrogen (N^{15}) after the feeding of glycine containing that isotope

In other studies London Shemin and Rittenberg found that N^{15} containing glycine became incorporated into the red cell hemoglobin of nucleated duck red cells and of human sickle cells in vitro Although they could not correlate this effect with the presence of young red cells (reticulocytes) Finch and his colleagues did so in similar experiments employing radioactive iron They and other workers also showed that vitamin B_{12} and pteroylglutamic acid directly promote the synthesis of hemoglobin by the nutritionally deficient erythroid cells of the bone marrow of patients with pernicious anemia To this specialized location for the synthesis of hemoglobin in the body the iron is transported bound to a beta globulin of the plasma after being absorbed in ferrous form and according to Granick temporarily combined in ferric form in the intestinal wall with the peculiar protein apoferritin

The classic method of estimating the rate of red cell destruction has been the determination of the output of fecal stercobilin presumably a quantitative derivative of hemoglobin However by the use of N^{15} containing glycine it now appears from the studies of London and his associates that at least 15 per cent of the stercobilin output in the normal individual is not derived from the breakdown of circulating hemoglobin In pernicious anemia this excess may amount to as much as 50 per cent It is thus possible that as was long ago suggested by Whipple bile pigment production may short circuit in part the insertion of hemoglobin into the finished red cell The work of Whipple and MacKenzie has clearly demonstrated that the normal spleen is a filter with capacity to distinguish and selectively to retain spheroidal as opposed to normally discoid red cells or according to Bjorkmann starch grains of 5 as opposed to 3 microns in diameter

From cross circulation experiments in leukopenic cats J S Lawrence has shown that leukocytes (in contrast to red cells) live only a few hours in the circulation being replaced on the

average about three times a day According to Jersild granulocytes younger than metamyelocytes are rarely phagocytic The endocrine system has been linked to leukocytosis by the demonstration of Cress and others that leukocytosis fails to appear after anoxia or convulsions in rats whose adrenal medullas have been removed Leukocytosis is seen however in the intact animal or in man after the administration of pituitary adrenocorticotrophic hormone Even in the absence of the adrenal medulla the injection of foreign protein causes leukocytosis probably because of liberation of the products of the inflammatory response that has been studied by Menkin The work of Dougherty and of White although not confirmed in all aspects postulates the lysis of lymphocytes in the nodes and in the circulation as a result of adrenocortical stimulation Clinically the eosinopenia resulting from the administration of pituitary adrenocorticotrophic hormone or of cortisone is even more striking in the normal subject It has been postulated that the lympholysis which occurs is a part of the alarm reaction of Selye and is beneficial to the organism by releasing antibody globulin from the lymphocyte The experimental work of Ehrich Kass Fagraeus and others has presented strong evidence that the responsibility for production of antibodies resides not as formerly supposed directly with the reticuloendothelial cells but rather with the lymphocytes or plasma cells of the lymphoid apparatus

A great deal of research has been reported in the field of blood coagulation rather to the confusion of the innocent bystander Out of the welter of terminology—different names for the same thing same name for different things—has emerged important new knowledge Tocantins did a service to clinical thinking in his article on hemostasis and its disturbances due to extravascular vascular and intravascular defects Lawrence using cross circulated irradiated cats concluded that platelets in circulation live from three to five days The Zuckers have shown us the platelets at work mechanically plugging the injured arterioles and apparently giving off vasoconstrictor substances in the process Jacques s introduction of silicone coated glassware has made it possible to handle blood in the laboratory almost as if it were still in the blood vessels and to separate by centrifugation various components without the deleterious influence of the wetted glass surface

The classic two stage concept of blood coagulation of Mora

witz became fundamentally modified by the clinical observations of Owren in 1944 In the study of a woman with a bleeding di athesis he discovered that the delayed prothrombin time of the blood could be returned to normal by the addition of traces of *prothrombin free normal plasma containing what he eventually* called factor V This accelerator of the conversion of prothrom bin to thrombin is either the same substance or if not possesses

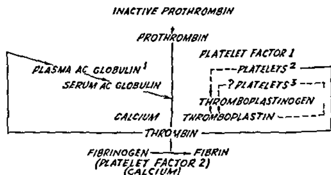


Fig 65—Bl d oagulat on an a to t lyt c e t n S eg rs Q ick M t e (Slightly mod fi d f om W J Ha ri gt figure)

an action similar to that of components of fresh plasma variously called labile factor accelerator globulin or serum pro thrombin conversion accelerator by others As a result the present concept of blood coagulation may be represented by the diagram shown in Figure 65

Against this background of increased knowledge of the physiology of blood have come important advances in pathology diagnosis and treatment of disorders of the red and white cells and of hemorrhagic diseases due to platelet or plasma abnor malities These will now be considered in this order

Red Cell Disorders

The decade opened with important discoveries The previous year Levine and Stetson had called attention to the role of the fetus in causing isoimmunization of the mother in pregnancy Wiener and *Peters then presented examples of hemolytic trans* fusion reactions resulting from sensitization to previous trans fusions with red cells containing the Rh factor In conjunction these discoveries led to understanding of the immunization re

actions responsible for erythroblastosis fetalis—antibody formation in the Rh negative mother bearing an Rh positive child with passage of antibodies into the fetal circulation via the placenta Today we know that no female who requires a transfusion is Rh negative and has not yet passed the menopause should be given Rh positive blood in any form unless her life is in immediate jeopardy

The working out of the complex genetic background of the allelomorphic genes of the Rh Hr system derives from the brilliant contributions of Fisher and Race Discovery by Race and by Wiener of the so called incomplete or blocking antibodies explained the frequent failure of maternal serum to agglutinate the red cells of the erythroblastotic infant in the conventional saline dilution system This obstacle was surmounted by working with suspensions of Rh positive cells in undiluted serum (Diamond) or in bovine or human albumin solution Coombs Mourant and Race devised a nonspecific but sensitive method of testing for the presence of antibodies adsorbed on the surface of washed red cells suspended in saline For this purpose they developed an antiserum in rabbits against human serum or human serum globulin This technic was useful not only in the study of erythroblastosis but even more so in the recognition of adsorbed proteins on the surface of the red cells of patients with so called acquired hemolytic jaundice Unfortunately no method of prevention has been successful but development of the exchange or exsanguination transfusion of Rh negative blood has been of therapeutic benefit to the severely affected infant Diamond recently reported the surprising observation that for this purpose the blood of female donors is especially useful

Acute blood loss from wounds was a major problem of the war The anticoagulant acid citrate dextrose solution greatly improved the viability of the red cells when subsequently transfused Group O blood not always a safe preparation for emergency transfusions because of a high agglutinating titer of the plasma against heterologous recipients cells was rendered safe by the addition of Witebsky s A and B substances derived from gastric tissue Where as in obstetric hospitals the risk of reactions or of immunization against the Rh factor is to be avoided at all costs universally safe blood is in addition required to be Rh negative Such improvements in technic together with the use of packed red cells (Mollison Alt) in severe anemias in

which the added plasma is a useless diluent highlight progress in the last few years Today the hazard of transmission of serum hepatitis especially by pooled plasma can be avoided by ultra violet irradiation or treatment with nitrogen mustard a method that can be applied even to whole blood

Much knowledge has been gained concerning the mechanisms of increased red cell destruction The occasional acute hemolytic anemia due to exposure to chemicals such as arsine naphthalene quinine acetanilid and sulfanilamide was shown by Emerson and Ham to result from injury to the red cells by oxidant derivatives of such drugs The oxidants tested were active even in vitro in increasing the mechanical fragility of red cells In severe burns the direct action of heat on the red cells caused similar increases in mechanical fragility

Demonstration of the short survival time of the red cells of congenital hemolytic jaundice in normal subjects by Dacie and Mollison and of sickle cell disease by Singer Moore and their respective associates clearly indicated a defective red cell perhaps because of its demonstrable increased mechanical fragility Owren has demonstrated that the so called familial or anemic crises in congenital hemolytic jaundice are in reality due to temporary inhibition of bone marrow activity rather than to increased red cell destruction In congenital hemolytic jaundice the increased mechanical fragility of the red cells results largely from changes in the cells occurring during sequestration in the spleen In sickle cell disease it is a direct physical result of the sickling process Sickling when the abnormal red cell is deprived of oxygen or exposed to reducing agents is ascribed by Pauling to an abnormal type of hemoglobin Harris has just demonstrated that even solutions of this hemoglobin exhibit orientation and alinement of the molecules when deoxygenated

In both thalassemia (Cooley s anemia) in which the causes of the abnormal red cell formation and destruction remain obscure and sickle cell disease a major and a minor form of the disorder have been recognized Genetic studies by Neel indicate that the severity of the pathologic manifestation in red cells of both diseases depends on whether the affected individual is hetero or homozygous for the special hereditary trait In paroxysmal nocturnal hemoglobinuria Ham has demonstrated an abnormality of the red cell that causes its lysis in native or foreign human plasma when slightly acidified The physiologic

increase in acidity of the blood especially in stagnant areas during sleep is presumably the cause of the nocturnally aug mented hemolysis

Abnormal plasma is now recognized as responsible for sev eral types of acquired hemolytic anemia The avidity of such plasma components for the red cells largely thwarted attempts at their demonstration in plasma until the positive reaction to the Coombs test shown to be characteristic of such patients by Boorman Evans and others led to more critical studies of plasma and tissues Dacie has recently described the presence in rare instances of a hemolysin active against all types of red cells when the serum is slightly acidified

It is well known that in many cases of acquired hemolytic anemia spontaneous agglutination of the red cells is observed This is frequently due to a cold agglutinin In many instances however as shown by Gardner there is an agglutinin demon strable at body temperature with augmentation when the serum is acidified Extending the concepts of Ham and Castle to the study of hemolysis in mismatched transfusion reactions occur ring without demonstrable hemolysins but with incompatible agglutinins Shen has shown in experimental animals that ag glutination alone results in sequestration of the red cells in the liver and other organs with subsequent i chemia and release of lytic substances from the tissues In patients with acquired hemolytic jaundice exhibiting a positive reaction to the Coombs test and autoagglutination of the red cells both phenomena are more marked in the blood in the splenic pulp than in blood in the periphery Wagley and others demonstrated further that the splenic pulp in such patients has the property of conferring a positive Coombs reaction on normal red cells Splenectomy in acquired hemolytic jaundice although not as in congenital hemolytic jaundice an almost certain cure may be beneficial This has been well demonstrated by Dameshek Splenectomy probably is effective because it removes an important source of abnormal agglutinin with avidity for the red cell and also elimi nates an organ capable of selective retention of agglutinated red cells with subsequent lysis Gardner has found that adreno corticotrophic hormone (ACTH) may temporarily halt a hemo lytic crisis and so make splenectomy feasible

During the decade a brilliant chapter of new knowledge con cerning nutritional macrocytic anemias was written with the aid

which the added plasma is a useless diluent highlight progress in the last few years Today the hazard of transmission of serum hepatitis especially by pooled plasma can be avoided by ultra violet irradiation or treatment with nitrogen mustard a method that can be applied even to whole blood

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avidity for vitamin B_{12} may not also help to condition the development of pernicious anemia The therapeutic activity of vitamin B_{12} is phenomenal in that 0 001 mg is apparently roughly equivalent to 1 U S P unit of liver extract when injected However vitamin B_{12} does no more (and also probably no less) as a therapeutic agent than does liver extract Its chief promise is its anticipated cheapness as a by product of antibiotic manufacture and its freedom from species sensitivity an effect sometimes observed with liver extracts

The studies of Bomford and Rhoads of so called refractory macrocytic anemias—disorders that came into prominence with the successful treatment of pernicious anemia and its relatives—constitute a classic description The patients display variability of bone marrow morphology from aplasia to hyperplasia and immaturity of the numerous cells In half the patients significant histories of exposure to cyclic compounds were obtained The histologic findings present a suggestive analogy to those of Hunter and Mallory in patients with chronic exposure to benzol In a few patients frank leukemia developed To the list of chemicals occasionally toxic to all elements of the bone marrow the decade added new substances such as atabrine* and tridione* Few advances in knowledge concerning other types of anemia beyond increased information about the appearance of the bone marrow as a result of the more frequent use of needle or trephine biopsy have been made For needle biopsy the iliac crest or vertebral spinous process is to be preferred to the sternum in the main for psychologic reasons Until recently studies of the effects of irradiation though actively pursued by many workers appear to have turned up little that is novel However Jacobson has just made the important observation that shielding of the spleen during irradiation of animals in some way promotes subsequent bone marrow recovery even though the spleen is soon removed

Shaefer has produced polycythemia in dogs by resection of the carotid and aortic depressor nerves The resulting neurogenic hypertension presumably causes a generalized peripheral vasospasm and hence stagnant anoxia of the bone marrow Renewed emphasis on the relation between myelogenous leukemia and polycythemia vera has been laid by several reports of patients whose disease progressed terminally to frank leukemia sometimes acute in type Because radiation is a slow acting leu

especially of microbiologic research In 1945 folic acid a growth factor essential for certain lactobacilli was made available in synthetic form by Angier and his associates for clinical trial Later its formula was disclosed as pteroylglutamic acid This yellow compound unexpectedly was found by Spies and later by others to be at least initially highly effective in all varieties of nutritional macrocytic anemia including pernicious anemia and sprue It was first thought to be the antipernicious anemia principle of liver but this belief was soon discarded because of its virtual absence in purified liver extracts With the aid of microbiology and of chromatographic separation of substances with a red color noted to be associated with clinical activity crystalline vitamin B_{12} was isolated from liver in 1948 almost simultaneously by the American Folkers and his associates and the British workers headed by Smith To Randolph West who with Dakin was a pioneer and later a persistent seeker of this goal went the honor of first demonstrating its clinical efficacy in pernicious anemia Subsequent work indicates that although folic acid fails in many instances to prevent or to arrest the development of spinal cord lesions in pernicious anemia vitamin B_{12} seems to be fully as satisfactory in this respect as is purified liver extract However in certain cases of nutritional macrocytic anemia usually associated with pregnancy and with grossly defective diets vitamin B_{12} like purified liver extract is devoid of activity In such patients orally administered crude liver extract or folic acid is gratifyingly effective Very recent clinical observations by Luhby and experimental work by May appear to indicate that the megaloblastic anemia of infancy is the result of a combined partial deficiency of folic acid and ascorbic acid

From the work of Berk Hall Bethell and others it appears that vitamin B_{12} is probably both the so called extrinsic factor and the antipernicious anemia principle of liver The role of the intrinsic factor of gastric juice thus appears to be specifically to promote the absorption of vitamin B_{12} from the alimentary tract In the broad tapeworm anemia of Finland according to Bonsdorff the worm when situated in the upper part of the alimentary tract is apparently able to inhibit the action of the small residual amount of the intrinsic factor characteristic of these patients Watson s recent studies with aureomycin raise the question of whether intestinal bacteria with demonstrable

duced with extracts of normal organs or with nucleic acid Thus it appears to resemble the occasional intense leukemoid reaction occurring in man from necrosis of tumors or other tissues The diagnosis of the type cell in blood samples bone marrow or lymph node biopsies continues to offer some indication of a better prognosis when well differentiated cells in patients in the older age groups are observed On the other hand the fluid evolutionary trends fast or slow to more malignant forms in the transitional histology of follicular lymphoma to Hodgkin s disease reticulum cell sarcoma or lymphosarcoma and lymphatic leukemia have been emphasized by Custer and Bernhard

The etiology of leukemia is a mystery its palliation a daily task its cure a fervent hope of many physicians It has become clear that the therapeutic effects of radioactive phosphorus (P^{32}) resemble closely those of x rays useful prolongation of life especially in chronic myelogenous leukemia little of value in acute forms and lymphomas It is thus not a significant addition to our therapeutic armamentarium albeit on occasion its less frequent dosage schedule is a convenience

The renaissance of interest in chemotherapy stems from the development of the so called nitrogen mustard war gases Of these methyl bis (β chloroethyl) amine hydrochloride (HN_2) is the most effective but must be given intravenously A recent modification (melamine) is given by mouth and is said not to cause the nausea and vomiting usually associated with the use of HN From the experience of Rhoads Dameshek Jacobson Wintrobe and others it appears that these compounds are particularly useful in Hodgkin s disease especially when x ray can no longer be tolerated or when there is diffuse visceral involvement or signs of intoxication The remissions induced appear quickly but are usually shorter than those caused by x ray Urethane therapy introduced in 1946 by Paterson was found to be particularly effective in chronic myelogenous leukemia Rundles and Moloney believe it also to be useful for multiple myeloma characterized by a fairly mature type of plasma cell The early hopes aroused by stilbamidine in this disease have not been fulfilled In acute leukemia of children Farber and his associates as well as others have observed partial or complete remissions in occasional cases of several weeks or even months duration from the use of analogues of pteroylglutamic (folic) acid Several workers have reported short remissions in acute leu

kemogenic agent it is highly unlikely that spray x ray or P[32] administration shortly preceding this development was a causative factor More probable is the supposition that the polycythemia was secondary to a latent and primary chronic myelogenous leukemia as may sometimes be the case in multiple myeloma

White Cell Diseases

Infectious lymphocytosis first described by Smith in 1941 has subsequently been reported by others as well in small epidemics among children and young adults The pronounced leukocytosis mostly of fully mature lymphocytes with little cytoplasm and a negative heterophil test chiefly distinguish it from infectious mononucleosis In the latter disease spontaneous rupture of the spleen has been reported several times The well recognized clinical appearance of jaundice in some patients was found by Peterson to be the expression of disturbed liver function occurring without visible jaundice in 20 of 40 patients A convenient rapid slide agglutination test with sheep cells has been devised by Moloney Hargraves has described the artificial production of the characteristic L E cell originally observed in bone marrow smears of patients with lupus erythematosus by incubation of plasma of these patients with bone marrow cells from individuals with unrelated conditions

In the prior decade the devastating effect of sepsis secondary to agranulocytosis itself due to drug sensitivity was clearly recognized Consequently when all methods of stimulating leukocyte production were found to be unreliable the discovery of the sulfonamides provided a direct attack on the infection This procedure introduced by Dameshek, was almost at once improved upon by the use of penicillin which lacked the leukotoxic properties observed with the sulfonamides in other patients Such a regime permitted spontaneous recovery to occur under its protection Several cases of cyclic leukopenia of uncertain origin have been reported as well as the neutropenia ascribed by Wiseman and Doan to splenic hyperfunction

Furth s expert review of experimental leukemia in 1946 provided a valuable documentation although many physician are skeptical of the analogy to the human diseases The myeloid metaplasia of the bone marrow described by Heinle and by Miller as produced in experimental animals given injections of extracts of the urine of patients with leukemia can al o be in

duced with extracts of normal organs or with nucleic acid Thus it appears to resemble the occasional intense leukemoid reaction occurring in man from necrosis of tumors or other tissues The diagnosis of the type cell in blood samples bone marrow or lymph node biopsies continues to offer some indication of a bet ter prognosis when well differentiated cells in patients in the older age groups are observed On the other hand the fluid evo lutionary trends fast or slow to more malignant forms in the transitional histology of follicular lymphoma to Hodgkin s dis ease reticulum cell sarcoma or lymphosarcoma and lymphatic leukemia have been emphasized by Custer and Bernhard

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kemogenic agent it is highly unlikely that spray x ray or P[32] administration shortly preceding this development was a causative factor More probable is the supposition that the polycythemia was secondary to a latent and primary chronic myelogenous leukemia as may sometimes be the case in multiple myeloma

White Cell Diseases

Infectious lymphocytosis first described by Smith in 1941 has subsequently been reported by others as well in small epidemics among children and young adults The pronounced leukocytosis mostly of fully mature lymphocytes with little cytoplasm and a negative heterophil test chiefly distinguish it from infectious mononucleosis In the latter disease spontaneous rupture of the spleen has been reported several times The well recognized clinical appearance of jaundice in some patients was found by Peterson to be the expression of disturbed liver function occurring without visible jaundice in 20 of 40 patients A convenient rapid slide agglutination test with sheep cells has been devised by Moloney Hargraves has described the artificial production of the characteristic L E cell originally observed in bone marrow smears of patients with lupus erythematosus by incubation of plasma of these patients with bone marrow cells from individuals with unrelated conditions

In the prior decade the devastating effect of sepsis secondary to agranulocytosis itself due to drug sensitivity was clearly recognized *Consequently when all methods of stimulating leukocyte* production were found to be unreliable the discovery of the sulfonamides provided a direct attack on the infection This procedure introduced by Dameshek was almost at once improved upon by the use of penicillin which lacked the leukotoxic properties observed with the sulfonamides in other patients Such a regime permitted spontaneous recovery to occur under its protection Several cases of cyclic leukopenia of uncertain origin have been reported as well as the neutropenia ascribed by Wiseman and Doan to splenic hyperfunction

Furth s expert review of experimental leukemia in 1946 provided a valuable documentation although many physicians are skeptical of the analogy to the human diseases The myeloid metaplasia *of the bone marrow described by Heinle and by* Miller as produced in experimental animals given injections of extracts of the urine of patients with leukemia can also be in

Measurable variations in platelet adhesiveness have been proposed by Wiener and by Moolten to explain lack of correlation between clinical bleeding and platelet levels in various types of thrombocytopenia Cryoglobulin as a cause of purpura of distal portions of the extremities has been ascribed by Lerner and Watson to local cooling with increase in blood viscosity or protein precipitation in the capillaries The use of antiheparin compounds (protamine and toluidine blue) in controlling bleeding as introduced by Allen is difficult to evaluate In a clinical study of the effects of splenectomy Robson clearly differentiated the prompt and nonspecific effects of the operation in shortening bleeding time and in increasing capillary resistance from the later rise of platelets which is possibly more specifically related to removal of the organ

According to Quick and Stefanini prothrombin A is removed from plasma by precipitation with tricalcium phosphate and is decreased by vitamin K deficiency (biliary obstruction or steatorrhea) liver disease and dicumarol® administration Prothrombin B is lacking in rare instances as a hereditary anomaly Labile factor disappears from plasma on standing has the various synonyms already referred to and is an even more rare congenital defect causing as do other types of prothrombin deficiency intermittent hemorrhagic phenomena Davidson and his associates recommend vitamin K_1 oxide as more efficient than simpler naphthoquinones in shortening the prothrombin time after dicumarol® overdosage

In hereditary hemophilia the earlier studies of Patek Taylor and their associates demonstrated a euglobulin in normal plasma capable of correcting the coagulation defect for several hours Its practical use in the form of fresh blood or plasma transfusions or of plasma fraction I of Cohn has been found by Frommeyer Epstein and Taylor to result in some patients in the evolution of a refractory state characterized by presence of an anticoagulant antibody in the patient s plasma Quick believes that the defect in hemophilia is one of plasma thromboplastinogen This being so even the normal platelet disintegration at the site of injury under the influence of thrombin does not result in normal blood coagulation

In patients other than hemophiliacs anticoagulant substances of a different character have occasionally been reported Heparin is said to have appeared in the blood of certain patients fol

kemia from adrenocorticotrophic hormone therapy after which the patient usually becomes refractory to this material

Because these various compounds exert profound effects on normal hemopoiesis and other body cell systems doubtless by inhibition of enzyme systems characteristic of many types of normal cells it is not surprising that their effects are relatively nonspecific in the treatment of disease and are accompanied by injury of normal tissues There can be no doubt however that there are specific biochemical differences between the neoplastic and the normal cell Their discovery will lead to far better control perhaps even cure of these conditions

Hemorrhagic Diseases

The question of whether the hemorrhages in thrombocytopenic purpura are due to abnormal capillaries as observed by MacFarlane or to defective mechanical plugging by platelets as noted by Zucker is not answered with finality Perhaps the normal platelet is in effect a potential partner in a durable capillary wall as is the mortar in a wall of bricks Quick and his associates have clearly demonstrated that thrombocytopenia leads to delay in the formation of a firm clot by failing to activate plasma thromboplastinogen The resulting lack of quantitative formation of prothrombin and therefrom of thrombin fails to provide the coarse fibrin strands essential to firm clot retraction and vessel sealing With thrombocytopenia the trivial amount of surface coagulation taken as the end point in the usual clotting time determination may be almost within normal time limits However it may be accompanied by little evidence of a significant continuing production of thrombin For this among other reasons Quick s prothrombin consumption (i e conversion to thrombin) test is a useful measure of the completeness of coagulation

In a study of the thrombocytopenic purpura not infrequently occurring with sedormid* (allyl isopropyl acetyl carbamide) therapy Ackroyd demonstrated local purpura with patch test and agglutination of the platelets by this and related open chain ureide compounds in plasma samples from sensitized individuals Since the first reports by Moschowitz and by Baehr and his associates several cases of an acute febrile usually fatal purpura associated with diffuse platelet thromboses of arterioles and capillaries have been described The etiology remains obscure

GENERAL CONSIDERATIONS

The articles selected for this section cover some general aspects of normal and pathologic physiology of the blood and blood forming organs The first five articles are concerned with basic processes in hemoglobin and red cell formation.—Ed.

Role of Oxygen in Regulation of Erythropoiesis Depression of Rate of Delivery of New Red Cells to Blood by High Concentrations of Inspired Oxygen. Oxygen tension of the environment is regarded as one of the principal regulators of rate of erythropoiesis This concept is based largely on the fact that stimulation of red cell formation regularly occurs at high altitudes or under conditions of decreased oxygen tension Evidence that the converse is true that high tensions of oxygen can decrease erythrocyte formation is more fragmentary A few experiments have demonstrated that animals become anemic within a few weeks when placed in atmospheres containing 60 per cent or more of oxygen at normal barometric pressure but definite evidence that such occurs in man has been obtained only in patients with sickle cell anemia John C Tinsley Jr Carl V Moore Reubenia Dubach Virginia Minnich and Moises Grinstein[1] (Washington Univ) attempted to demonstrate that the phenomenon was a general one and not limited to sickle cell anemia

Oxygen was administered continuously for 8-14 days through a meter face mask to two patients with sickle cell anemia one with congenital hemolytic anemia four with untreated pernicious anemia and two men with late syphilis in whom red cell equilibrium was normal

With oxygen concentrations of 50 per cent or more in the inspired air the following evidences of erythroid depression were regularly observed In chronic hemolytic anemia during the oxygen period there were dramatic decrease in number of reticulocytes fall in red cell count of approximately 1 000 000 cells and a slower rate of radioactive iron utilization for hemoglobin synthesis After oxygen was discontinued decided reticulocytosis developed red cell count returned rapidly to control level and utilization of radioactive iron was accelerated In patients with pernicious anemia injection of

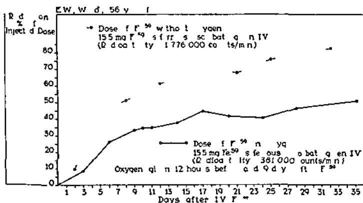
(1) J Cl I t g t on 28 1544 1564 N mbe 1949

lowing irradiation or the administration of HN_2 In contrast to other hemorrhagic disorders the characteristic tendency to bleeding in the joints of hemophiliacs and the lack of correlation between coagulation time and bleeding manifestations have perhaps at last received an explanation Thus the work of Tocantins and of Soulier appears to indicate a relative deficiency of tissue thromboplastin in hemophilia Soulier found no such difference as exists normally between the prothrombin time of venous and of capillary blood presumably because in the hemophiliac the capillary blood is not significantly contaminated with tissue thromboplastin as a result of the needle puncture

In rare congenital instances such as that reported by Corbett the blood fails entirely to clot because fibrinogen is almost completely or even entirely absent from the blood Adequate coagulation can temporarily be achieved with transfusions or better intravenous administration of fraction I of Cohn containing fibrinogen Following surgical or hemorrhagic shock or particularly premature separation of the placenta (Wiener) severe bleeding may occur and samples of the patient s blood are found to coagulate briefly and then again to liquefy This is due to the presence of fibrinolysin recently studied by MacFarlane and by Tagnon among others The phenomenon of fibrinolysis is presumably the result of activation of an enzyme precursor by products of tissue autolysis

—William B Castle

oxygen o curred without any alteration in pH of arterial plasma and in the absence of toxic manifestations The mecha nism by which oxygen tension of environment affects erythro poiesis is not known The most commonly held theory is that one of the factors which controls red cell production is oxygen tension in marrow itself Since chronic hypoxia is associated with secondary polycythemia it is assumed that the resultant low oxygen tension in marrow stimulates erythrocytogenesis



F g 67 —Ut l f F⁵⁹ f h m gl b y th by m l lj t d g t l p od d d g h l t f 70 pe t yg (C t f T l y J C J et l J Cl 1 t g t 28 1544 1564 N emt 1949)

Conversely if erythroid tissue is exposed to an increased oxy gen tension rate of red cell formation would be expected to de crease The authors results are compatible with this idea

Hemin Synthesis in Spleen Homogenates It has been demonstrated that the alpha carbon atom of glycine is incor porated in the hemin and globin moieties of the hemoglobin molecule when glycine labeled with C^{14} in the methylene car bon atom is fed to rats Hemin synthesis in vitro has also been demonstrated in several instances Since there exists histologic evidence of extramedullary hemopoietic activity in the spleen Kurt I Altman and Kurt Salomon (Univ of Ro hester) thought it of interest to test with biochemical methods the possibility of hemin synthesis from labeled gly cine in spleen homogenates

METHOD —A spleen homogenate from three rabbit spleens was

( ) Sc 3 117 118 F b 3 1950

therapeutic doses of liver extract or of vitamin B_{12} while high concentrations of oxygen were being given caused a sub maximal reticulocyte response (Fig 66) During the post oxygen period a second reticulocyte crisis larger than the first occurred in each instance In subjects with normal blood formation radioactive iron injected intravenously during oxygen administration was delivered to peripheral blood as newly formed hemoglobin at a rate distinctly less than nor

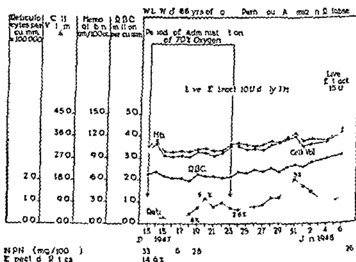


Fig 66 — Eff t f 70 p t yg n th peut e p n t l (Co t y of T l y J C J t l J Cl J st g t 28 1544 1564 \ l t m 6 1949)

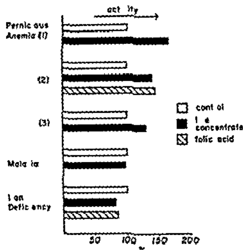
mal (Fig 67) There was also a small but definite decrease in reticulocytes which corrected itself after oxygen was re moved Several weeks after these observations utilization of radioactive iron was again studied so that each subject *could* serve as his own control Curves obtained in the second study fell within the normal range There remained no doubt *therefore* that utilization of iron was depressed during oxy gen administration

These data indicate that oxygen breathed *in* concentrations of 50 per cent or more depresses rate of erythropoiesis in nor mal human subjects in patients with chronic hemolytic ane mias and in patients with pernicious anemia This effect of

in the red cell stroma capable of removing iron from the serum and (2) the synthesis of heme

Similar incubation studies were conducted on bone marrow aspirations Uptake of radioiron by normoblasts was much greater than that in reticulocytes Again radioactive heme could be demonstrated after incubation of radioiron with marrow cells

Radioiron can be used as an indicator of altered hemopoiesis (Fig 68) Suspensions of marrow from patients with



F g 68 —M w ac bat Eff t f f (d and l M w ll bta ned by st nal p t on f m p t ent w th t ted per m h wed crease d ptak f 66 44 d 28 p ent f dd tion f 0 00001 t f } 5 μg f l a d (Court y f W l b R J t al Sci 110 396-398 O t 14 1949)

untreated pernicious anemia repeatedly showed an acceleration of the rate of iron uptake after addition of liver or folic acid compared with control studies This did not occur in conditions other than those characterized by specific deficiencies of the substances used These observations indicate that liver and folic acid act directly on immature erythrocytes of marrow cells in untreated pernicious anemia

[However recently Horrigan and Vilter have found that vitamin B₁₂ but not folic acid is active when injected *locally* n maturing the megaloblasts of the bone marrow of the il ac crest n pern cious anemia —Ed.]

prepared glycine labeled with C^{14} in the methylene carbon atom was added and the homogenates were then incubated for appropriate periods After addition of crystalline hemin as carrier either hemin or protoporphyrin IX dimethyl ester was isolated and determination of C^{14} activity was carried out with an ionization chamber apparatus

Results indicated that hemin synthesis can be carried out by rabbit spleen homogenates utilizing the methylene carbon atom of glycine as a precursor

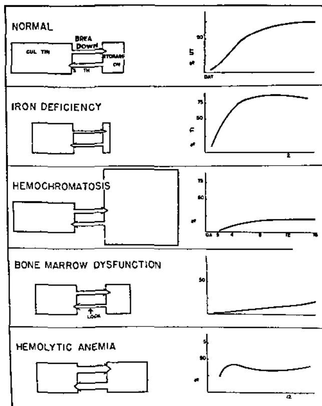
Iron Metabolism Heme Synthesis in Vitro by Immature Erythrocytes Studies with radioiron have indicated that there is no exchange of iron between the mature erythrocyte and surrounding plasma R J Walsh E D Thomas S K Chow R G Fluharty and C A Finch[3] present data however which indicate that reticulocytes assimilate iron and synthesize heme in vitro and that this uptake of radioiron may be used as an indicator of the rate of hemoglobin synthesis In vitro studies using Fe^{59} and Fe were performed in rocking boats at 37 C in a gas mixture of 95 per cent oxygen and 5 per cent carbon dioxide

Whereas blood containing less than 1 per cent reticulocytes took up no measurable quantity of radioiron uptake was demonstrated repeatedly in blood with a high reticulocyte count It was shown that radioactivity was localized in the immature cells by correlating reticulocyte count and radioactivity in various fractions of this blood Blood was studied from individuals with various types of anemia including iron deficiency acquired hemolytic sickle cell and pernicious anemia Uptake of iron in all instances was attributable to presence of reticulocytes It further appeared that at least in pernicious anemia rate of uptake was also related to the type of reticulocyte present The early reticulocytes after liver therapy contained more reticular material and picked up more radio activity

To determine whether the uptake of iron indicated hemoglobin formation red cells were fractionated after incubation with radioiron The greatest activity in the reticulocyte portion was found in stroma of hemolyzed cells However significant amounts of radioiron were also demonstrated in recrystallized heme from these cells These observations indicate that the physiologic process of assimilation of iron by the developing red cell is (1) the attachment of iron to acceptors

(3) Science 110 396-398 Oct 14 1949

Among eight patients with viral bacterial and protozoal in fections utilization curves were extremely depressed in those severely ill One patient with sickle cell anemia one with congenital hemolytic anemia and three with acquired hemo



Fg 69 (C rt y f F h C A t l Blood 4 905 9 6 A g t 1949)

lytic anemia showed a rapid initial utilization rate and max imal values were obtained in three to five days However total amount of iron in the circulation was low Of three pa tients with pernicious anemia two were given radioiron before liver therapy was effective and utilization was retarded In the third however radioiron administered several days after

Iron Metabolism Utilization of Intravenous Radioactive Iron Iron is rigidly conserved by the body and no attention need be directed to its excretion in absence of blood loss This conservation emphasizes the importance of the metabolic cycle in the body in which iron is used again and again for hemoglobin formation Clement A Finch John G Gibson II Wendell C Peacock and Rex G Fluharty[4] studied the dynamic relation between storage and circulating iron in normal subjects and in patients with various hematologic disorders When single tracer doses of radioactive iron (Fe and Fe^{59}) are given intravenously to man radioiron rapidly enters the hemoglobin cycle and tagged erythrocytes appear in the circulation within 24 hours Thereafter radioactivity of circulating red cells rises and reaches a plateau in two to three weeks This procedure appears to offer a method of measuring participation of injected iron in the hemoglobin cycle The term utilization curve subsequently used refers specifically to utilization of injected radioiron for hemoglobin production In most experiments Fe^{55} (half life four years) was used Two to three weeks after injection venous blood samples were obtained in the morning and hematologic studies done

Over 15 18 days eight normal controls showed utilization of between 68 and 83 per cent (average 74 per cent) Three patients with diseases not expected to alter iron metabolism (diabetes myocardial infarction and asthma) had utilization curves similar to the composite curve of normal subjects

Six patients with acute or chronic blood loss representing varying degrees of iron deficiency as shown by the degree of microcytosis and hypochromia showed rapid utilization of injected radioiron Utilization curves of three patients with hemochromatosis confirmed by liver biopsy were depressed in presence of fairly normal red cell production In one patient with refractory anemia and hyperplastic bone marrow one with acute disseminated lupus erythematosus and aplastic marrow and one with extensive lymphosarcomatous involvement of bone marrow only small amounts of radioiron appeared in peripheral blood Curves of five patients with renal disease and some anemia thought to be due to the uremic state were depressed below normal

(4) Blood 4 905 9 6 A gu t 1949

that life span of erythrocytes may be limited at least in part by changes within the cell which render it more susceptible to destruction by mechanical wear and tear in the circulation It is emphasized however that trauma produced by rolling glass beads may be quite unlike that to red cells in vivo

Decrease in circulating radioactive iron was observed in each experiment soon after mechanical fragility of tagged

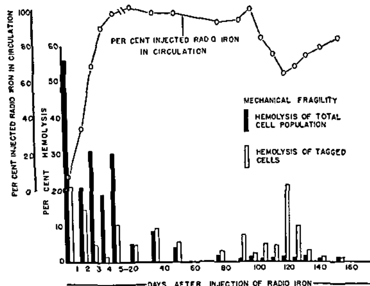


Fig 70 (C t y f Stew t W B *et al* J E p M d 91 147 159 F bru ary 1950)

cells began to exceed that of total cell population The lowest point on the curve representing circulating radioiron was noted at 119 119 and 122 days respectively after injection of iron in three experiments Estimates of the life span of dog erythrocytes obtained in this way agree with those pro vided by other methods

[From these careful observations and from those of Shen and his associates demonstrating increased mechanical fragility of the red cells of patients with certain types of hemolytic anemia (congenital sickle cell d sease etc) it is reasonable to assume that th s factor is an impo tant one in determ ning the life of the red cell —Ed]

liver therapy was utilized rapidly and an early plateau reached Utilization curves of two patients with carcinoma were depressed and those of four patients with typical Addison s disease were within normal range

In interpretation of utilization curves there are two important components size of iron stores and bone marrow function Figure 69 depicts the storage and circulating red cell iron in certain conditions as compared with typical radio iron utilization curves In hemochromatosis and iron deficiency the primary factor influencing utilization was size of iron stores In hemolytic anemia and bone marrow dysfunction the chief factor was rate of blood production in bone marrow With a normal rate of blood production changes in percentage utilization reflect alteration in iron stores If storage iron is not greatly altered percentage utilization is determined by function of erythropoietic tissue Rate of erythropoiesis may be estimated by the slope of the utilization curve and evidence of abnormal red cell destruction is found in an early and abrupt plateau of the utilization curve

Age as Affecting Osmotic and Mechanical Fragility of Dog Erythrocytes Tagged with Radioactive Iron W B Stewart J M Stewart M J Izzo and L E Young[6] (Univ of Rochester) administered radioactive iron to three normal dogs two of which had previously been bled *in order to* tag a group of erythrocytes of approximately known age Osmotic fragility of newly formed tagged cells was significantly greater than that of the general cell population during the first few days after injection of the iron while the mechanical fragility of the young cells was less than that of the general red cell population Figure 70 illustrates the mechanical fragility of tagged dog erythrocytes and of total cell population at various intervals after injection of radioactive iron Circulating radioiron at each interval is expressed as percentage of dose injected As the cells aged and approached the end of the life span their susceptibility to destruction by trauma inflicted by rolling glass beads exceeded that of the general cell population Osmotic behavior of the old cells was not distinctive

Increased mechanical fragility of senescent cells suggests

(6) J E per M d. 91 147 159 F bru ry 1950

an optimal concentration of calcium is essential Thrombo plastin is also needed Accelerator globulin is a plasma protein which acts as a cofactor of thromboplastin for rapid activa tion of prothrombin a deficiency may result in a bleeding tendency

Platelets also furnish material which participates in pro thrombin activation but contrary to the view held for many years they probably do not furnish much thromboplastin activity The activity is more nearly like that supplied by Ac globulin i e in conjunction with thromboplastin

The exact function of Ac globulin in the clotting mecha nism has not been definitely established However several sound experiments indicate that Ac globulin probably partici pates in prothrombin activation in the following manner First a small amount of prothrombin is activated by calcium platelet accelerator and thromboplastin The small amount of thrombin formed activates plasma Ac globulin Then a rapid interaction of prothrombin thromboplastin calcium platelet accelerator and active Ac globulin occurs Thrombin is thus formed rapidly after a slow beginning Quantitative methods have been developed for measuring Ac globulin activity in plasma Such methods reveal that man possesses a lower concentration of Ac globulin than other species The con centration decreases in experimental liver damage tem porarily in dicumarol[8] therapy and slowly in citrated human plasma after 10 days of storage With large doses of amino phylline Ac globulin concentration in the plasma may double

Under certain conditions calcium thromboplastin Ac globulin platelet derivatives and other factors are prevented from contributing to prothrombin activation by any of several inhibitors The best known inhibitor is heparin

The mechanism for clot removal is strikingly similar to the clotting one A plasma substance profibrinolysin is ac tivated to fibrinolysin and this enzyme can dissolve a fibrin clot

Platelet Thrombosis in Human Hemostasis Histologic Study of Skin Wounds in Normal and Purpuric Individuals The importance of blood platelets and platelet thrombosis in the hemostatic mechanism of rats was recently demonstrated In view of the frequency of species variation in anatomy and physiology evidence for or against a comparable role of

Budding of Thrombocytes from Megakaryocytes Previous studies reported that 0 43 75 per cent of megakaryocytes show thrombocyte budding Ronald H Girdwood[7] (Simpson Memorial Inst Ann Arbor Mich) determined the percentage of megakaryocytes showing budding by various technics The accuracy of different technics was evaluated and the actual percentage of such megakaryocytes determined as conclusively as possible

When marrow aspirations were performed using a syringe flushed with sodium citrate a false impression was obtained because many thrombocytes were washed away from parent cells When the dry technic was used results were equally inaccurate because thrombocytes in juxtaposition to megakaryocytes sometimes stuck to them appearing to arise from them When aspirated marrow samples were used best indication of the extent of budding was obtained with a dry technic limiting examination of marrow to areas with definite marrow structure It is concluded that less than 25 per cent of megakaryocytes in normal marrow show true budding at any one time

↓ The following seven abstracts deal with rapidly developing concepts in the field of blood coagulation Other articles with more specific relation to hemorrhagic diseases will be found in appropriate sections —Ed

Blood Coagulation and Practical Significance of Recent Advances in Knowledge of Prothrombin and Ac Globulin are discussed by Walter H Seegers[8] (Wayne Univ) It is advantageous to consider blood clotting as if two mechanisms are provided one involving the interaction of proteins which effects clot formation and one for clot removal

Prothrombin is constantly present in blood if an adequate amount of vitamin K is available for its synthesis by the liver In clot formation prothrombin must first be activated to form thrombin Thrombin reacts with fibrinogen of the plasma to form fibrin which is the clot Calcium tends to have a favorable influence on this process but is not essential Material of platelet origin also makes it much easier for thrombin to clot fibrinogen

In prothrombin activation a number of substances participate calcium thromboplastin accelerator globulin platelet derivatives and other factors For physiologic activation

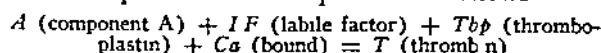
(7) P oc Soc E per Bi l & Med 7 192 195 O t be 1949
(8) C culat n I 9 J ry 1950

easy reading even in abstract form and the original texts by masters in the field deserve perusal —Ed]

State of Component A (Prothrombin) in Human Blood Evidence That It Is Partly Free and Partly in Inactive or Precursor Form The old classic theory that prothrombin is converted by thromboplastin (thrombokinase) and ionized calcium to thrombin has become untenable because of recent findings A new factor essential for thrombin formation has been discovered It is called the labile factor and is a constituent of both plasma and serum It loses activity when heated and is diminished in stored plasma because of oxidation

During work which led to discovery of the labile factor it was observed that when stored oxalated human plasma was mixed with an equal volume of dog plasma in which prothrombin had been reduced by dicumarol® or adsorbed to aluminum hydroxide the resulting mixture had a prothrombin time shorter than that of fresh plasma Later it was found that human citrated plasma often showed a reduction in prothrombin time after 24 hours of storage No explanation for these findings could be offered until it was recognized that two changes were concurrently taking place in stored plasma a decrease in labile factor and an increase in some other factor which augmented prothrombin activity Owing particularly to development of an assay method for component A (component A of prothrombin probably corresponds to the classic prothrombin) and to discovery of the effect of silicone coated containers on prothrombin activity during storage data have been obtained which not only offer an explanation for the increased prothrombin activity of aged plasma but a new concept concerning the state of prothrombin in blood

From studies based on the prothrombin time of plasma and from data obtained with the adsorption and elution of component A Armand J Quick and Mario Stefanini[1] (Marquette Univ) conclude that formation of thrombin requires component A the labile factor thromboplastin and combined calcium The equation can be expressed as follows



A (component A) $+ IF$ (labile factor) $+ Tbp$ (thromboplastin) $+ Ca$ (bound) $= T$ (thrombin)

The reaction appears to follow the law of mass action There is no evidence that any of the factors are accelerators

(1) J Lab & Cl Med 34 1203 t 15 Septemb 1949

platelets in spontaneous human hemostasis would have interest particularly since few observations on man's hemostatic mechanism have been published Technical difficulties in microscopic observation of human vessels during arrest of hemorrhage have not been overcome though observations on animals have been reported

Howard D Zucker[9] (Mount Sinai Hosp New York City) studied serial sections of biopsy specimens of human skin and subcutaneous fat containing puncture wounds after measurement of local bleeding times Specimens were obtained from three patients with normal hemostasis and four with idiopathic thrombocytopenic purpura

Agglutinated platelets arrested hemorrhage in normal skin by rapidly sealing the mouth of all cut vessels larger than capillaries Such platelet thrombi resisted the effective blood pressure in a cut arteriole of 55 μ diameter The puncture tract was normally filled with red cell fibrin clot into which platelet thrombi protruded The red clot sealed the mouth of the few opened capillaries which could be identified Other capillaries may have been sealed by endothelial agglutination Fibrin did not enter or form in injured vessels

Platelet thrombosis was not seen in specimens from patients with idiopathic thrombocytopenic purpura When larger arterioles and venules were cut bleeding was greatly prolonged and fibrin failed to form in the wound because of the speed of blood flow When smaller vessels were cut bleeding time was moderately prolonged but the vessels were eventually sealed by fibrin alone Bleeding time was normal if only capillaries were cut because these were sealed by fibrin

The similarity of histologic appearance described here to that reported after experimental vascular injury in other mammals suggests considerable similarity in mammalian hemostatic mechanisms

Zucker emphasizes that clinical bleeding time tests vary greatly in depth of puncture and in caliber and number of vessels cut Considerable volume of hemorrhage during the first minute is the best guide to an adequate test of the entire hemostatic mechanism

[This article emphasizes the long suspected mechanical importance to hemostasis of platelet agglutination The next four articles do not make

(9) Blood 4 631 645 My 1949

Nature of Action of Labile Factor in Formation of Thrombin was investigated by Armand J Quick and Mario Stefanini (Marquette Univ) It is accepted that in addition to thromboplastin and calcium a third factor is required for thrombin formation *It is called the labile factor because it* loses activity on storage Prothrombin time is proportionately delayed as this factor is diminished which suggests that thrombin production is reduced However the theoretical objection can be raised that if the factor acts as an accelerator prothrombin activation would only be slowed The procedure developed recently for isolating and assaying free prothrombin by adsorption to tricalcium phosphate and elution with sodium citrate offers a direct approach for determining whether or not the labile factor acts stoichiometrically or as an accelerator The authors therefore devised the following experiment To stored oxalated plasma a fixed excess of thromboplastin an optimal quantity of calcium and varying amounts of labile factor were added Fibrin was removed and prothrombin remaining in the serum was estimated by the adsorption and elution method Thereby the effect of the labile factor on prothrombin consumption was quantitatively determined since the other agents in the reaction were kept constant

Results revealed that when excess thromboplastin and an optimal amount of calcium were added to stored oxalated plasma only a little prothrombin was consumed On adding increasing quantities of labile factor in the form of diluted deprothrombinized rabbit plasma prothrombin consumption was progressively increased This indicates that the role of the labile factor in thrombin formation like that of thromboplastin and calcium is stoichiometric

Role of Calcium in Coagulation of Blood Introduction of two technics using silicone (methylchlorosylone General Electric Dri Film 9987) a film which keeps blood incoagulable without alteration of its properties or lysis of platelets and Amberlite IR 100 (Resinous Products & Co Philadelphia) a resin which quantitatively removes calcium from the blood has offered new possibilities for study of the role of calcium in blood clotting With a combination of these technics it is possible to obtain in vitro blood which differs from that cir

( ) Am J Phy 1 160 572 575 M b 1950

In fresh human plasma component A (prothrombin) is present partly free and partly in an inactive or precursor state which corresponds to the proserozyme of Bordet Activation requires a rough surface but there is no evidence that calcium (as Bordet assumed) thromboplastin or thrombin is essential for conversion to the active state Thus in oxalated human plasma (without ionized calcium) nearly all of component A is changed to the active form after 24 hours of storage if kept in contact with a rough surface such as glass

In coagulation of plasma with a deficiency of available thromboplastin due either to a lack of thromboplastinogen as in hemophilia or to removal of platelets concentration of free component A is greatly increased because little of the original active form is consumed and additional active component A is produced from the inactive precursor

Two types of congenital hypoprothrombinemia are known in which a deficiency of component A occurs In one a true deficiency of both free and total component A exists In the other which is more common and is hereditary concentration of total component A is normal but the amount of free or active component is below normal When these two types of deficient plasma are mixed the prothrombin time of the mixture becomes normal This suggests that a mechanism completely unknown regulates the ratio of active to total component A

The present work confirms early conclusions of Bordet that serozyme or prothrombin may exist in an inactive or precursor state but unlike Bordet's concept that all exists as proserozyme present observations show that a large fraction of total component A is in an active form It appears probable that in a number of recent studies activation of component A has been misinterpreted as an acceleration of conversion of prothrombin to thrombin Since the procedure of the two stage method for determining prothrombin is such that all of component A is converted to the active form this method determines total prothrombin (component A) but does not distinguish between the free and the inactive form The one stage method on the contrary determines the free or active component A and to determine the total all of component A must first be converted to the active state

concluded that combined and not ionized calcium is the fraction active in blood coagulation

Fibrin, a Factor Influencing Consumption of Prothrombin in Coagulation The prothrombin consumption test as originally described determines prothrombin activity remaining in serum one hour after coagulation By means of this test it was established that little prothrombin activity is lost when either platelet poor plasma or hemophilic blood clots These results are explained by postulating that in hemophilia a marked deficiency of thromboplastinogen exists so that only a small amount of prothrombin can be converted to thrombin In thrombocytopenia the platelet enzyme required for activation of thromboplastinogen to thromboplastin is lacking therefore little thromboplastin can become available and consequently little prothrombin is consumed Since the prothrombin consumption test is promising as an important clinical test Armand J Quick and Jean E Favre Gilly[4] (Marquette Univ) attempted to find why at times erratic results were obtained

When normal human blood is allowed to clot and to stand for one hour more than 60 per cent of prothrombin is usually consumed as measured by prothrombin time of serum Serum obtained from clotted blood before retraction occurs has a strikingly short prothrombin time immediately after centrifugation which quickly becomes prolonged showing that there is rapid decrease in prothrombin after separation of serum from the clot If sodium citrate is added to clotted blood before centrifugation the serum obtained has a normal prothrombin time of 11 12 seconds which indicates that the abnormally short prothrombin time of serum immediately after centrifugation is due to a summation of thrombin formed during centrifugation and the amount produced during the prothrombin test

The insignificant consumption of prothrombin in unretracted clotted blood is explained by the rapid and complete adsorption of the freshly formed thrombin by the fibrin clot with its large adsorptive surface that is in intimate contact with the dispersed serum The continuous adsorption of thrombin prevents initiation of the autocatalytic reaction of coagulation which is mediated through the labilizing action

(4) Am J Phy l 158 387 395 S ptembe 1949

culating in vivo only in its complete lack of calcium Addition of measured amounts of calcium under different experimental conditions then permits accurate study of its influence on different phases of coagulation and on the process in toto

Using these new technics Mario Stefanini[3] (Marquette Univ) found the calcium level optimal for coagulation of whole blood or of plasma to be about 1 5 mM practically identical with that of circulating blood that for optimal conversion of prothrombin to thrombin is about 2 5 10 mM Though calcium is the most effective clotting agent its action *is not specific since strontium and to a lesser extent magne*sium possess similar activity All these cations exercise an inhibitory effect at concentrations higher than the optimal one

All three phases of coagulation appear to be influenced by calcium in artificial experimental conditions Optimal activation of thromboplastin in vitro as expressed by results of the prothrombin consumption test requires a CaCl concentration of 8 12 mM optimal action of thrombin on fibrinogen takes place at CaCl levels lower than 5 mM Calcium is most active in the phase of clotting leading to formation of thrombin from prothrombin

Decrease of prothrombin activity due to progressive disappearance of the labile factor and rise of antithrombin activity during storage are closely related to presence or absence of calcium as they are maximum in plasmas made incoagulable with addition of sodium oxalate or sodium citrate 0 02 M or by passage through highly active Amberlite and much less pronounced in plasmas made incoagulable with sodium citrate 0 01 M or by passage through only partially active Amberlite This influence of calcium on the stability of the labile factor seems to indicate existence of a calcium labile factor complex

Stefanini presents evidence that sodium oxalate acts as an anticoagulant not only by precipitating calcium but also by removing the metal from combination with a factor indispensable for blood coagulation and that sodium citrate inhibits coagulation by combining with one or more factors of the prothrombin *complex in which it can be substituted by* any bivalent cation (Ca Sr Mg) From this evidence it is

(3) Acta med. Scand na 136 250 266 1950

convert prothrombin to thrombin nor clot fibrinogen Further more preparations of plasma globulin were said to be separable into two fractions one which promoted clotting and one which exhibited proteolytic activity

Since none of the reported experiments conclusively demonstrated that proteolysis is essential in physiologic clotting of blood the authors made further investigations They prepared a fraction of globulin from human plasma which was deficient in prothrombin thrombin fibrinogen plasma thromboplastin and accelerator globulin but contained considerable potential proteolytic activity which could be activated by streptococcus fibrinolysin This fraction accelerated clotting of normal platelet deficient plasma However the clot accelerating effect of the globulin fraction was the same whether or not its proteolytic property had been activated Addition of streptococcus fibrinolysin to normal platelet deficient plasma did not accelerate coagulation Nor did addition of streptococcus fibrinolysin to hemophilic platelet deficient plasma promote its coagulation

These data suggest that proteolysis by activated plasma proteolytic enzyme is not an essential stage in blood coagulation The possibility cannot be excluded that the precursor of plasma proteolytic enzyme may promote blood clotting even though it is apparently proteolytically inactive in respect to fibrinogen prothrombin and casein

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HEMOLYTIC ANEMIAS

The following articles are concerned with anemias in which red cell destruction exceeds the capac ty of the bone marrow to manufacture them The first three are concerned with eryth oblastosis fetalis —Ed

Studies on Preventive and Curative Treatments for Rh Sensitization Rh antibodies are not found preformed but may appear as a result of active or passive sensitization Active sensitization may develop after repeated intravenous or subcutaneous injections of Rh positive blood into an Rh negative person or as the result of pregnancy and escape of Rh positive cells of the fetus into circulation of an Rh negative mother Passive sensitization occurs if antibodies from a sensitized mother pass through the placenta into the circula

of thrombin on platelets Fibrin therefore appears to be the most important physiologic antithrombin

It seems clear then that fibrin puts the brake on the autocatalytic reaction of coagulation and keeps it localized to the area in which vascular damage has occurred Paradoxically the fibrin clot which is feared most in thromboembolic diseases is perhaps the most important protection against extension of thromboses beyond the area that requires the thrombi to effect hemostasis It may be postulated that clot retraction in vivo may be dangerous since the extruded serum separated from intimate contact of the adsorptive surface of fibrin will allow thrombin to form which immediately causes extension of intravascular clotting If this assumption is correct factors favoring clot retraction such as anemia and rise in number of platelets increase the danger of progressive intravascular clotting

Studies on Proteolytic Enzyme in Human Plasma Relation between Proteolytic Activity of Plasma and Blood Coagulation Oscar D Ratnoff Robert C Hartmann and C Lockard Conley[5] (Johns Hopkins Univ) point out that evidence has been offered both to support and to deny the hypothesis that activated proteolytic enzyme of plasma accelerates blood clotting It has been reported that serum becomes proteolytic after addition of chloroform and again that chloroform treated serum is capable of clotting solutions of fibrinogen The chloroform activated proteolytic property of plasma was shown by one investigator to be present in its globulin fraction Others stated that proteolytic properties of plasma globulin can be activated not only by chloroform but by bacteria free filtrates of cultures of beta hemolytic streptococci A fraction of plasma globulin activated by streptococcus fibrinolysin was found to be thromboplastic hence it was concluded that the proteolytic enzyme of plasma plays a role in blood clotting Further evidence suggesting a relation between proteolysis and coagulation was that inhibitors of trypsin inhibited activity of proteolytic enzyme of plasma and also inhibited blood coagulation

On the other hand certain data cast doubt that proteolysis plays any physiologic role in clotting In particular it was reported that purified proteolytic enzyme of plasma did not

(5) J E pe Med 91 123 133 F bru ry 1950

the importance of priming It is thought that they should be primed against the bacterial antigen before they have opportunity to be primed against the Rh antigen thus making certain that the vaccine is the more potent antigen Fifty eight patients were multiparas Of the entire group one patient despite countersensitization showed Rh antibodies Nine women sensitized by previous pregnancies were also treated but the practice has been discontinued since experience showed that vaccine therapy was of no avail If the value of vaccine therapy can be established it will be as a preventive measure for those who still show no evidence of sensitization Although the evidence seems to warrant belief that this therapy may reduce incidence of sensitization to the Rh factor it is not infallible More experience is needed

Use of the so called hapten produced by Carter was also studied It is obtained from an ethereal extract of Rh positive cells which is next reduced to dryness and the residue dissolved in alcohol It is assayed for potency by two methods complement fixation and direct inhibition of agglutinins and administered intramuscularly Rh hapten appears to be a lipid substance which does not produce antibodies when injected into the experimental animal To test this material 130 injections were given 11 patients Results were negative

When Rh *sensitization is extreme the only recourse for* couples desiring children is to adopt a child or resort to artificial insemination from an Rh negative donor or if the husband is heterozygous to take the chance that the next baby may be Rh negative If sensitization is mild it may be possible to save the baby by inducing labor prematurely and giving the infant exchange transfusion without delay

Erythroblastosis Fetalis Value of Blood from Female Donors for Exchange Transfusion In reviewing 208 cases of erythroblastosis fetalis treated by exchange transfusion Fred H Allen Jr Louis K Diamond (Harvard Univ) and Joseph B Watrous Jr[8] (Boston Lying in Hosp) noted that although mortality was 15 1 per cent in the whole group no deaths occurred in the 42 babies who received blood from female donors exclusively This finding prompted statistical analysis of the available data in this large series

In 179 cases blood was used exclusively from male donors

(8) New England J Med 241 799 806 N 24 1949

tion of the fetus Lester J Unger[6] (New York Univ Bellevue Med Center) reports on efforts made to meet the problem of active sensitization by the Rh factor

New rules have been established for selection of donors for transfusion Rh positive blood should be given to all Rh positive patients (except newborn infants with erythroblastosis due to Rh sensitization) Only Rh negative blood should be given to all Rh negative females from birth to the climacteric For Rh negative women after the climacteric and for Rh negative males of any age Rh positive blood may be given when necessary provided it is recognized that Rh antibodies may develop and provided subsequently the proper pretransfusion tests are performed If sensitization results only Rh negative donors may be used for all subsequent transfusions

The problem of sensitization due to pregnancy is not as simple as the similar problem with transfusion Three methods of treating the mother were studied (1) repeated partial replacement transfusions (2) countersensitization with bacterial vaccines and (3) treatment with hapten It seemed reasonable that repeated partial replacement transfusions might possibly reduce or at least prevent a rise of titer of antibodies in the blood of a mother sensitized by the Rh factor To test this method four women were treated All showed Rh antibodies in the serum two had anti Rh agglutinins and two had Rh blocking antibodies In each case 500 cc blood was withdrawn and 500 cc transfused and repeated until the total amount decided on had been removed and replaced Amount varied from 6 500 cc in 11½ weeks to 21 000 cc in 14½ weeks In no case was there appreciable change in Rh antibody titer despite use of these enormous amounts of Rh negative blood

The second mode of therapy undertaken was that of countersensitization Because of experimental evidence supporting the theory of competition of antigens because of lack of danger with use of typhoid and pertussis vaccines and because any immunity developed by the mother would be of value to the infant clinical trial was begun two years ago At present 93 Rh negative women have been or are being treated by countersensitization Even though the first pregnancy is nearly always spared 26 primiparas were treated because of

(6) Am J Obst & Gynec 58 1185 1 00 December 1949

of the newborn Adult plasma or serum causes pronounced agglutination of red cells which are coated with the blocking antibody It is thought therefore that transfusion of erythro blastotic children with adult s whole blood may be contrain dicated because the infused adult plasma may activate the in complete antibody present in the baby

On the basis of this reasoning Pennell treated 28 patients with erythroblastosis fetalis by transfusion of compatible sedimented red cells from bank blood Three (10 7 per cent) died The mortality rate compares favorably with that in other reports on exchange transfusion

Transfusion of sedimented red cells to the erythroblastotic infant has a number of advantages Severe anemia is overcome by a comparatively small volume (50-60 cc) of cells which cannot overburden the infant s circulatory system The pro cedure for administering the sedimented cells is simple can be carried out via a scalp vein in 15 20 minutes does not re quire special equipment or specially trained transfusion teams and is available wherever there is a blood bank Furthermore it eliminates administration to the infant of large amounts of extraneous substances such as sodium citrate heparin and calcium gluconate which are employed in exchange trans fusion The amount of adult plasma which sedimented red cells contain is about 5 per cent and is probably much too small to cause activation of any agglutinins which might be present in the infant The fact that the infant s coated cells are allowed to remain seems of no consequence

Hereditary Nonspherocytic Hemolytic Anemia There are three well known and well defined types of hereditary hemolytic anemia hereditary spherocytosis sickle cell anemia and Mediterranean anemia In addition several other types of inherited anemia have been identified in recent years [The author gives appropriate references to these in the orig inal article —Ed] William H Crosby[1] (Brooke Gen l Hosp Fort Sam Houston) studied a form of hereditary nonsphero cytic and normochromic hemolytic anemia transmitted as a mendelian dominant and associated with brachyphalangia and porphyria Attention was directed to the family through one of its members a soldier

Blood of 35 of the patient s relatives was examined A

(1) Blood 5 33 2 3 M h 1950

(137 cases) or from female donors (42 cases) Of the 137 babies who received blood from male donors only 27 died (19 7 per cent) All 42 who received blood from female donors survived The difference in mortality rates is statistically significant Analysis of other factors such as sex of the infant severity of illness the mother s anti Rh titer and length of gestation showed that no other factor could be held responsible for the benefit of blood from female donors Though further statistical data may possibly not substantiate these results the present study indicated that the beneficial effect of a large amount of blood from female donors in babies with erythroblastosis fetalis is statistically striking In addition to the original series of 179 13 babies with erythroblastosis fetalis were deliberately treated with exchange transfusion using blood from female donors There were no deaths The beneficial component of such blood is unknown but isolated plasma fractions are being investigated It appears that for the present exchange transfusion using blood from a female donor is the treatment of choice

Treatment of Erythroblastosis Fetalis by Transfusion with Sedimented Red Cells is reported by Samuel Pennell[9] (Maimonides Hosp Brooklyn) Treatment by exchange transfusion is predicated on the suppositions that (1) if Rh antibodies particularly of the incomplete or blocking variety can be demonstrated in the mother ante partum the child when born will usually have severe erythroblastotic disease (2) replacement of the affected infant s blood at birth with normal blood by exchange transfusion removes the passively transferred antibodies and the child s damaged red cells thus avoiding hemolysis and arresting progress of the disease In the light of more recent information these hypotheses appear to need re evaluation Rh negative mothers showing high Rh antibody titers ante partum may give birth to Rh positive infants in whom severe erythroblastosis does not develop even though Rh antibodies derived from the mother can be demonstrated both attached to their red cells or circulating freely in their plasma Incomplete or blocking Rh antibodies require an activator which is supplied by both human serum and bovine albumin to effect agglutination of red cells This activator is diminished to an ineffectual level in the plasma

(9) Blood 5 107 12 F bru ry 1950

after splenectomy and four months after operation the count had risen to 45 per cent in the peripheral blood and to 56 per cent in the bone marrow In tests which involved mechanical vacuum and osmotic injury the patient s cells showed normal resistance Fragility tests which involved incubation showed uniformly an increased sensitivity of the patient s cells as compared with those of normal controls but compared with those of spherocytic controls the sensitivity was not so great Cross incubation experiments showed the patient s cells to be equally sensitive in his own serum or that of a group compatible control Preliminary heating of the serum for 10 minutes reduced the hemolytic potency about 50 per cent It could not be reactivated by addition of guinea pig complement This observation suggests presence of a heat labile hemolytic factor in serum to which the patient s red cells were sensitive Such a reaction rather than a structural weakness may be the basis of the short survival time of red cells in this disease The patient s cells survived only 12 days when transfused into a normal compatible recipient When normal compatible cells were transfused into the patient attrition occurred at a normal rate Neither degree of anemia nor rate of hemolysis was favorably influenced in the patient by splenectomy

Of the hereditary anemias this disease seems most closely to resemble hereditary spherocytosis Yet differences of cellular survival in vivo and in vitro and failure of splenectomy in hereditary nonspherocytic hemolytic anemia suggest a difference in the hemolytic mechanism Demonstration of porphobilinogen in this patient suggests a possible relation of this hereditary hemolytic anemia to hereditary porphyria

Acute Hemolytic Anemia Due to Naphthalene Poisoning was observed in four children aged 2 2½ by Wolf W Zuelzer and Leonard Apt (Wayne Univ) All patients had eaten or sucked moth balls containing naphthalene Initial symptoms were listlessness and anorexia followed by emesis fever abdominal pain and pallor Icterus and splenomegaly were either absent or mild Hemoglobinuria was observed in three patients The basic pathologic process was a severe acute hemolytic anemia evidenced by low hemoglobin level erythrocyte count and hematocrit with increased erythrocyte saline fra

(2) J A M A 141 185 190 Sept. 17 1949

reticulocyte count was used as a screening test since persons with familial anemia may have a normal red cell count Physical examination was performed on those persons showing reticulocytosis who consented to it After short fingers were encountered several times it was recognized that brachyphalangia was also a familial characteristic With the information obtained it was possible to construct a fair pattern of the disease as it affected members of this family There was a low grade normochromic anemia which did not vary greatly in intensity from one person to another Slight jaundice was also present Affected men were all heavy laborers unaware of their jaundice and unhampered by their anemia Spleen was enlarged in all instances Liver was enlarged in older persons the degree of enlargement apparently increasing with age Bouts of abdominal pain with onset always after age 20 had been experienced by most of those with anemia The reason for pain was not clear In two persons gallstones had been diagnosed yet removal of the gallbladder in one case did not end the abdominal pain There was no history of leg ulcer nor except for a cerebrovascular accident in the grandfather had there been thrombotic or hemorrhagic incidents

Genetic study revealed that the anemia and deformity of the hands were transmitted as mendelian dominant characteristics In no instance had an unaffected person transmitted either trait to his offspring Though these abnormalities did occur in the same person they also occurred independently and were not genetically linked Neither condition was sex linked It appeared that anemia was somehow associated with blood group A since each person with demonstrated anemia was of that group Genetic linkage cannot account for association of group A blood and anemia

Red cells on stained spreads appeared normally filled with hemoglobin Morphologically the cells were normal biconcave disks In the patient and other affected members of the family the following procedures were negative test for abnormal hemolysins and agglutinins including the Coombs antiglobulin test for incomplete antibodies tests for cold agglutinins and cold hemolysins and the Ham acid fragility test for paroxysmal nocturnal hemoglobinuria Before splenectomy the iron stain showed less than 0 1 per cent siderocytes in the patient s peripheral blood Siderocytes gradually increased

probably the direct action of absorbed naphthalene on the red cell membrane

[Emerson and Ham have shown that the hemolytic action of certain coal tar drugs is due to the formation of oxidant derivatives which in vitro cause increases in the osmotic and mechanical fragility of the red cells —Ed]

Marchiafava Micheli Syndrome (Paroxysmal Nocturnal Hemoglobinuria) John Marks[3] reports 3 cases and reviews the 73 previously reported The Marchiafava Micheli syndrome is one of the rarer types of hemoglobinuria characterized by the usual features of hemolytic anemia with hepatosplenomegaly and bouts of hemoglobinuria A distinctive feature is that the hemoglobin is either present in urine only during sleep or else increases greatly during sleep as compared with waking The patient s cells are hemolyzed by his own and by normal serum and the reaction is sensitive to changes in pH This specific serologic test is known as Ham s test

The di ease is neither hereditary nor racial nor is it related to occupation Males and females are affected equally The disease may begin at any age but is commonest between 20 and 40

The disease does not always present primarily with hemoglobinuria Presenting symptoms in the 73 cases recorded in the literature were hemoglobinuria in 33 cases jaundice in 27 anemia or dependent symptoms in 36 lumbar pain in 7 abdominal pain in 5 and splenomegaly in 2 It is clear therefore that in hemolytic anemia absence of hemoglobinuria does not exclude the Marchiafava Micheli syndrome It is advisable to include the specific serologic test in investigation of any obscure hemolytic anemia irrespective of the presence of hemoglobinuria

Cause of the disease is unknown The primary fault appears to be in the erythrocytes there being no evidence of inherent abnormality in the serum Autogenous cells are hemolyzed by autogenous serum and by normal serum to the same extent whereas autogenous serum does not hemolyze normal red cells Previous exposure to cold is not necessary to initiate hemolysis The hemolytic reaction is sensitive to changes in pH within the range of changes which may occur in the body The hemolysin is thermolabile and heated serum will inacti

(3) Q rt J M d 18 105 1 1 Ap 1 1949

gility reticulocyte count and nucleated red cells Leukocytosis anisocytosis poikilocytosis microcytosis spherocytosis and free hemoglobin in plasma were always noted There was pronounced fragmentation of red blood cells (Fig 71) Heinz bodies in erythrocytes were seen in blood smears in the one case in which a search was made on admission

Results of tests for isoagglutinins autoagglutinins cold agglutinins cold and warm hemolysins were negative No in



Fig 71—Bl od m (W ght t) h w g p d f agm t t n f e yth o yt \ t g l o tl f f gme t d ll th co ce t at n f h mo- gl b n n o d nd the fa t t f th ppo te le (C u t sy f Z el W W d Apt L J A M A 141 185 190 S pt 17 1949)

fectious process was found in the children and all recovered after blood transfusions Splenectomy is contraindicated If *hemoglobinuria is present alkalinization of the urine* may be indicated It is difficult to differentiate this disease from Lederer s anemia unless a history of naphthalene ingestion is elicited

Similar changes were obtained in dogs fed naphthalene appearance of Heinz bodies preceding onset of hemolytic anemia Heinz bodies were also produced by exposing normal canine erythrocytes to plasma of dogs fed naphthalene

The mechanism of the intravascular hemolysis which is the cause of the acute anemia of naphthalene poisoning is

bins of normal persons and of persons with sicklemia and sickle cell anemia This report deals largely with an electro phoretic study of these hemoglobins

Results indicate that a significant difference exists between electrophoretic mobilities of hemoglobin from erythrocytes of normal persons and from those of persons with sickle cell anemia The two types of hemoglobin are easy to distinguish *as the carbonmonoxy compounds at pH 6 9 in phosphate* buffer of 0 1 ionic strength In this buffer the sickle cell an emia carbonmonoxyhemoglobin moves as a positive ion whereas the normal compound moves as a negative ion there is no detectable amount of one type present in the other The hemoglobin from erythrocytes of persons with sicklemia however appears to be a mixture of normal and sickle cell anemia hemoglobins in roughly equal proportions The elec trophoretic difference between normal and sickle cell anemia carbonmonoxyhemoglobin also exists in the ferrohemo globins Experiments with a buffer different from the phos phate demonstrated that the difference between the hemo globins is essentially independent of the buffer ions

The most plausible hypothesis for the cause of the differ ence in mobilities is that a difference in number or kind of ionizable groups exists in the two hemoglobins Experiments indicated that sickle cell anemia hemoglobin has 2-4 more net positive charges/molecule than normal hemoglobin Stud ies have been initiated to elucidate the precise nature of this charge difference and it appears probable that normal and sickle cell anemia hemoglobin have different globins

Since hemoglobins in sickle cell anemia and sicklemia erythrocytes *are different from those present in normal red* cells it appears probable that the hemoglobins are responsible for the sickling process The mechanism of the sickling process may be pictured as follows It is proposed that a surface re gion on the globin of the sickle cell anemia hemoglobin mole cule is absent in the normal molecule and has a configura tion complementary to a different region of the surface of the hemoglobin molecule The fact that sickling occurs only when partial pressures of oxygen and carbon monoxide are low sug gests that one of these sites is near the iron atom of one or more of the hemes and that when the iron atom is combined with either of these gases the two structures are complemen

vate normal serum Hemolysis increases greatly during normal sleep whatever the time of day An increase in blood acidity during sleep has been suggested as the salient feature of the disease although the evidence is contradictory Hemolysis may be inhibited in vitro by presence in plasma of the following substances sodium citrate potassium oxalate potassium cyanide and heparin Concentration of the ions of some of these substances changes during sleep and these changes rather than pH changes may be responsible for the nocturnal character of the hemoglobinuria

No cure has been reported and no treatment has given lasting improvement Although the reason is unknown para sympathomimetic drugs seem to decrease the hemoglobinuria and therefore seem worthy of further trial The course is irregularly downhill over 7 10 years with death usually from intercurrent infection Splenectomy is contraindicated the operation has a 40 per cent mortality and has never been re ported to cure In addition to the acid serum hemolysis test of Ham the heat test of Hegglin and Maier is a *specific* test for Marchiafava Micheli syndrome [because during incubation glycolysis increases acidity of the blood —Ed]

Sickle Cell Anemia A Molecular Disease Erythrocytes of certain individuals possess the capacity to undergo reversible changes in shape in response to changes in partial pressure of oxygen With lowered pressure these cells change from the normal bioconcave disk to crescent holly wreath and other forms a process known as sickling About 8 per cent of American Negroes possess this characteristic usually they exhibit no pathologic consequences and are said to have sicklemia or sickle cell trait However in about 1 in 40 a severe chronic anemia results from excessive destruction of erythrocytes this is sickle cell anemia The main observable difference between erythrocytes of sickle cell trait and sickle cell anemia is the greater reduction in partial pressure of oxygen required for sickling of a major fraction of trait cells than for anemia cells Because evidence indicated that sickling may be intimately associated with the state of hemoglobin in the erythrocyte Linus Pauling Harvey A Itano S J Singer and Ibert C Wells[4] (California Inst of Technology) compared the physical and chemical properties of hemoglo

(4) Science 110 543 548 Nov 25 1949

blood counts were possible only when warm pipets and diluting fluid were used Mild hypochromic anemia developed

In February 1948 salicylate therapy (5 2 Gm sodium salicylate daily in divided doses) was begun with the hope of blocking antigen antibody reaction At this time cold agglutinin titer was 1 20480 One week later the titer was 1 10,240 and plasma salicylate level 24 8 mg /100 cc Subsidence of titer was difficult to evaluate however because of a sudden period of warm weather and improvement was not maintained

It is suggested that the primary mechanism responsible for symptoms due to presence of cold hemagglutinins is intravascular clumping of erythrocytes The precipitating factor is presumably cold This possibility should be considered in cases of bilateral gangrene in which exposure to cold alone has not been severe enough to produce this pathologic process Local thrombosis of a deep part is more difficult to explain but the primary mechanism is thought to be probably the same Hemoglobinuria results whenever tubular absorption falls behind filtration rate

Use of salicylates was suggested by experimental work on animals given sodium salicylate orally and at the same time immunized by intravenous injections of bacteria Such rabbits showed diminished complement fixing antibodies agglutinins and hemolysins when compared with controls Anti Rh agglutinin formation in guinea pigs and rabbits is reduced when sodium salicylate is administered before and during immunization with rhesus monkey blood cells It has also been shown that when typhoid vaccine is given patients receiving massive salicylate therapy antibody formation is suppressed

[A cold hemolysin was not excluded as the cause of hemoglobinuria and anemia in Case 2 because the Donath Landsteiner test was not performed Howeve the hemolysis in this patient was probably due to the increased mechan cal fragility of the cold agglutinated red cells by the high t ter of the plasma cold agglutinin as experimentally demonstrated by others in such patients —Ed.]

Developing (Coombs) Test in Spherocytic Hemolytic Anemias Its Significance for Pathophysiology of Spherocytosis and Splenic Hemolysis The developing (Coombs) test using an anti human globulin rabbit serum demonstrates globulin antibodies adsorbed to the surface of erythrocytes Thus coated and uncoated red cells can be distinguished Karl Singer and Arno G Motulsky[6] (Michael Reese Hosp

(6) J Lab & Cl M 34 768 783 J n 1949

tary to a considerably diminished degree The sickle cell anemia hemoglobin molecules might then be capable of interacting with one another at these sites sufficiently to cause at least a partial alinement of the molecules within the cell with the result that the erythrocyte becomes birefringent and the cell membrane is distorted to accommodate the now relatively rigid structures within its confines

[Our associate John W Harris has just demonstrated that 15 25 per cent solutions of deoxygenated hemoglobin from sickle cells exhibit increase in viscosity birefringence and tactoid formation These are direct evidences of molecular alinement and aggregation—Ed]

Symptoms Attributable to Cold Hemagglutination Report of Two Cases is made by Jeanne C Bateman[5] (Washington D C) Presence of cold hemagglutinins should be suspected when there is difficulty in blood counting procedures or cross matching of blood at room temperatures or when acrocyanosis hemolytic anemia and hemoglobinuria follow exposure to cold As pointed out by Stats and Wasserman gangrene may develop if exposure is prolonged Less commonly thrombotic phenomena are manifest

CASE 1 —Man 22 was hospitalized with complaints of a chilly feeling fever malaise increasingly severe nonproductive cough and dyspnea There were moist rhonchi and fine rales in both lung fields Cultures of blood and sputum were negative White cell count was 6 500 Twelve hours after he was placed in an oxygen tent signs and symptoms of thrombophlebitis developed in the superficial veins of the right leg It was noted that the oxygen tent was unusually chilly The patient gradually recovered At no time did he receive sulfonamide therapy Cold hemagglutinin titers were 1 1,280 the 6th day after admission 1 2 560 the 11th day and 5 weeks later had dropped to 1 640

CASE 2 —Man 43 first experienced purplish blue mottling of face ears and fingers after exposure to cold in November 1944 Symptoms were followed by passage of red urine The patient s condition was diagnosed as kidney disease and he was at bed rest for two months Symptoms reappeared when he was permitted to go outdoors but subsided during the following summer only to reappear with onset of cold weather There was no history of primary atypical pneumonia or of other viral infection Physical examination was essentially noncontributory except for demonstration of acrocyanosis following exposure to cold

In April 1946 when he was first seen by Bateman cold hemagglutination titer was 1 2 621 440 During the next two years there was a wavelike decline in titer with a tendency for titer to be lowest during the summer However thermal range remained so wide that

(5) A ch. J t Med 84 5 3 531 Octobe 1949

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(6) J Lab & Cl M d. 34 768 783 J 1949

Chicago) report 16 cases of hereditary and acquired spherocytic hemolytic anemia studied with antiglobulin serum. All seven with idiopathic acquired type and one with symptomatic hemolytic anemia (reticulum cell sarcoma) gave a positive reaction. It was negative in one patient with hemolytic anemia caused by a sulfonamide. Of the seven patients with hereditary spherocytosis, six showed a negative reaction and one severely ill patient had a strongly positive reaction. Splenectomy in the acquired disease resulted in disappearance of the coated spherocytes, or the coated cells remained demonstrable although the pathologic hemolysis ceased. Splenectomy in the patient with hereditary spherocytosis and a positive Coombs reaction led to disappearance of the coating although spherocytosis persisted. This demonstrated that two different mechanisms were operating in this case.

A positive reaction indicates presence of immune bodies. The immune bodies which occur in spherocytic anemias are qualitatively different from the antibodies directed against Rh Hr antigens.

Existence of 'coated' and 'uncoated' spherocytes is explained by the hypothesis of the multiple origin of spherocytes. In the hereditary type of hemolytic anemia uncoated cells develop in the marrow under genetic control, whereas in the immunologic variety spherocytes are formed after contact with coating antibodies originating in the spleen and/or other organs. Spherocytosis caused by physical and chemical factors results from exposure of normal red cells to these agents either intravascularly or within damaged tissues.

The theory of specific splenic hemolysis is advanced to explain the role of the spleen in spherocytic hemolytic syndromes in contrast to the current hypotheses of hypersplenism. According to the hypothesis of specific splenic hemolysis the spleen participates little if at all in physiologic red cell disintegration. Recent studies have shown that physiologic erythrocyte elimination depends on cell age and the mechanical factors to which it is exposed during its life span within the circulation. All hemolytic syndromes are characterized by erythrocytes with specific structural alterations of the cytoskeleton. Such changes may manifest themselves either morphologically or functionally. Splenic hemolysis is predominantly involved in the spherocytic hemolytic

syndromes In the hereditary disorder the spleen selectively removes the uncoated pathologic cells In the immunologic acquired variety the spleen produces the coating antibodies which it is assumed injure the cells and thus render them spherocytic Conceivably the cells may then be destroyed in the spleen by an increased concentration of antibodies in this organ

It is well known that patients with acquired hemolytic anemia may or may not respond to splenectomy whereas patients with the hereditary disorder almost always benefit

DEVELOPING TEST IN HEMOLYTIC ANEMIAS

P R CT

A Acquired spherocytic hemolytic anemias
  1 Idiopathic
  2 Symptomatic (Hodgkin s disease leukemia lymphomas Boeck s sarcoid Gaucher s disease * ovarian tumors * etc)

B Hereditary spherocytosis (occasionally)

C Isoimmunization due to known immune bodies Rh Hr A B (M*)
  1 Erythroblastosis fetalis
  2 Sensitization following transfusion

NEG TIVE REA

A Hereditary spherocytosis

B Spherocytic anemia due to physical or chemical factors (burns * sulfonamides phenylhydrazine*)

C Sickle cell anemia

D Cooley's anemia

E Paroxysmal nocturnal hemoglobinuria

A sum d n b f th d

Patients with the acquired disorder may be classified into three groups according to their response to splenectomy In the first group spherocytes disappear completely and permanently In the second the coated cells persist pathologic hemolysis stops and the spherocytes have a normal life span in the patient and even when transfused into a normal person. In the third group coated spherocytes continue to be destroyed rapidly These different responses require an explanation

In the first group antibody production is apparently restricted to the spleen A persistently positive Coombs reaction after splenectomy indicates that antibodies are manufactured in other organs as well The fact that splenectomy stops the pathologic hemolysis in some of these patients and does not in others may perhaps be explained on a quantitative basis If formation and release of damaging immune bodies proceed on a larger scale in extrasplenic tissues splenectomy will

Chicago) report 16 cases of hereditary and acquired sphero cytic hemolytic anemia studied with antiglobulin serum All seven with idiopathic acquired type and one with symptomatic hemolytic anemia (reticulum cell sarcoma) gave a positive reaction It was negative in one patient with hemolytic anemia caused by a sulfonamide Of the seven patients with hereditary spherocytosis six showed a negative reaction and one severely ill patient had a strongly positive reaction Splenectomy in the acquired disease resulted in disappearance of the coated spherocytes or the coated cells remained demonstrable although the pathologic hemolysis ceased Splenectomy in the patient with hereditary spherocytosis and a positive Coombs reaction led to disappearance of the coating although spherocytosis persisted This demonstrated that two different mechanisms were operating in this case

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Existence of coated and uncoated spherocytes is explained by the hypothesis of the multiple origin of spherocytes In the hereditary type of hemolytic anemia uncoated cells develop in the marrow under genetic control whereas in the immunologic variety spherocytes are formed after contact with coating antibodies originating in the spleen and/or other organs Spherocytosis caused by physical and chemical factors results from exposure of normal red cells to these agents either intravascularly or within damaged tissues

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Repeated blood examinations revealed severe macrocytic anemia with erythrocyte counts of 1 000 000 1 500 000 and hemoglobin value of 3 5 5 5 Gm There was reticulocytosis of 25 50 per cent and a raised mean corpuscular volume Reaction to the Coombs test was positive and cold autohemagglutinins were present to a titer of 1 512 at 2 C there was just perceptible autohemagglutination at 37 C Plasma bilirubin level was raised

Hemolysis continued at an extremely rapid rate and blood transfusions were of only transient benefit Hemoglobinuria was generally absent but was observed on several occasions after transfusions Data obtained by the differential agglutination technic confirmed that transfused blood was rapidly eliminated

It was repeatedly found that normal group O erythrocytes and the patient s own corpuscles underwent hemolysis in vitro in the patient s serum The hemolytic antibody seemed to be distinct from the cold hemagglutinin antibody and was absorbed onto corpuscles better at 37 C than at lower temperatures Amount of hemolysis was largely determined by pH of the corpuscle serum suspension Hemolysis was maximal at about pH 6 8-7 0 and was inhibited below pH 6 and above pH 8 there was but a trace of hemolysis in unacidified serum This restricted pH hemolysis range seemed due to the hemolysin s being poorly absorbed at the alkaline side of neutrality When graded amounts of acid were added to serum it could be shown that the pH range within which hemolysis could be observed corresponded closely to that in chronic hemolytic anemia with nocturnal hemoglobinuria

Although the cause was obscure there can be little doubt that this patient had a severe idiopathic acquired hemolytic anemia The abnormal hemolysis in the patient s serum was an unusual feature It is probably only in the severest forms of hemolytic anemia when autoantibodies are being formed in large amounts that there is sufficient for detention in serum over and above that absorbed onto the patient s own corpuscles This probability and the fact that adjustment of pH to an optimum for hemolysis is important in demonstration of hemolysins of the type described perhaps accounts for the rarity of similar observations

Acquired Hemolytic Anemia Relation of Erythrocyte Antibody Production to Activity of Disease Significance of Thrombocytopenia and Leukopenia are discussed by Robert S Evans and Rose T Duane[8] (Stanford Univ) It has been increasingly evident that acquired hemolytic anemia is caused by a hemolysin active for all erythrocytes whereas congenital hemolytic jaundice is due to a defect in red cell

(8) Blood 4 1196 1213 N mbe 1949

not be successful However understanding of these mechanisms is too incomplete to rule out the possibility that qualitative differences in coating antibodies and their associated damage to the cytoskeleton may not also be of importance

Demonstration of a positive reaction to the Coombs test in hereditary hemolytic anemia diminishes the value of this test in differential diagnosis between hereditary and acquired spherocytic anemia Since a positive reaction indicates an immunologic mechanism a negative reaction speaks strongly for familial spherocytosis if drugs and other obvious hemolytic agents can be ruled out The table summarizes the disorders in which performance of the developing test may be of diagnostic value The authors believe that the developing test is essential in diagnosing hemolytic syndromes If the reaction is positive the hemolytic anemia should be designated as of the immunologic type Such an immunologic hemolytic anemia may even be superimposed on hereditary spherocytosis

[We are in substantial agreement with this excellent article However it is not necessary to assume that because globulins are adsorbed on red cells they are antibodies In many instances substances have an avidity for the red cell merely because of a particular molecular structure e g certain viruses The Coombs test tells us only that a globulin is adsorbed The reason it is there may be quite different in different diseases The strongly positive Coombs reaction in the single case of congenital hemolytic jaundice may readily be interpreted as evidence of a superimposed acquired process —Ed]

Hemolysins in Acquired Hemolytic Anemia Effect of pH on Activity in Vitro of Serum Hemolysin Hydrogen ion concentration has a controlling effect on many hemolytic systems both simple and complex Effect of pH or carbon dioxide concentration on activity in vitro of hemolytic antibodies of human origin has seldom been considered except in the case of chronic hemolytic anemia with nocturnal hemoglobinuria in cold hemoglobinuria and in a case of acute hemolytic anemia in infancy J V Dacie[7] (Postgraduate Med School of London) reports observations on the activity in vitro of an abnormal hemolysin in the serum of a patient with idiopathic acquired hemolytic anemia and the effect of pH on its action

Girl 18 severely ill was hospitalized with signs of intense hemolysis Splenectomy had been performed for hemolytic anemia about five years before Cause of the original hemolytic attack was uncertain family history did not suggest a familial incidence

(7) Bl od 4 928 934 A gu t 1949

like agent in all The data are summarized in the table Diagnosis of hemolytic anemia was based on presence of chronic anemia reticulocytosis an increase in serum bilirubin and in most patients demonstration of increased fecal urobilinogen In most instances patients did not exhibit well marked spherocytosis and increased osmotic fragility In further dis

TYPICAL HEMATOLOGIC DATA IN RELATION TO AGGLUTINABILITY OF ERYTHROCYTES IN DILUTIONS OF ANTIGLOBULIN SERUM

P t No	St D ase	H m tocrit	% Reticulocyte	Icte cs In	F al U i L nor	G tes D lutio o A t ul n S um Show i g Agg u tin
1	Active	21	8 0	30	2080	1—320
	Quiescent post splenectomy	41	1.2	5	175	1—20
2	Active	28	270	100		1—640
3	Active	26	18 0	20	450	1—160
	Spontaneous remission	36	170	10		1—10
4	Active disease after splenectomy	17	70 0	40		1—160
5	Active disease after plenectomy	26	20 0	30	700	1—320
6	Quiescent after sple nectomy	40	1 0	10		1—40
7	Active	23	12 0	10	1560	1—320
	Quiescent 3 mo post splenectomy	33	1 6	8	220	1—1
8	Active	34	13 0	20	1800	1—80
	Spontaneous remission	45	1 0	10		1—5
9	Quiescent 18 mo post splenectomy	47	0 5			1—5
10	Quiescent 12 mo post splenectomy	42	4 0		306	1—5
11	Active	28	22 0	30		1—640

tinction to congenital hemolytic jaundice rapid destruction of normal transfused cells was evident in seven patients (Fig 72)

The sensitizing agent was found to be adsorbed on erythrocytes when it could not be demonstrated in serum The amount adsorbed was assayed roughly by making serial dilutions of the antiglobulin serum With this technic a fairly consistent correlation was found between the amount of antibody on the cell and activity of the disease Splenectomy when successful exerted a curative effect by sharply reducing amount of antibody substance on the cell Two patients entered spontaneous remission after a long period of activity Onset of re

structure During the last few years it has been possible to demonstrate sensitization of erythrocytes from patients with acquired hemolytic anemia with immunologic technics developed in the field of Rh sensitization There is some evidence by analogy that the hemolytic agent in acquired hemolytic anemia is an immune body similar to the univalent or hyperimmune Rh antibody and may be a response to antigen stimulus

The destructive agent appears to be a fraction of plasma protein probably a globulin similar to the univalent or hyperimmune Rh antibody Because accelerated hemolysis proceeds at a fairly constant rate in acquired hemolytic anemia it appears that the agent does not require special conditions of temperature or pH for activity The sensitizing agent can be removed from the surface of the red cell by heating a suspension of sensitized cells in normal saline The immune body appears to remain active to some degree in the saline eluate because normal cells exposed to it become agglutinable in the Coombs reagent The agent is thought to be active for all erythrocytes because transfused cells seem to be destroyed at a rate which approximates rate of destruction of native cells

Although the etiologic significance of the antibody like abnormality in acquired hemolytic anemia seems established study of patients who appeared to have recovered completely following splenectomy showed persistence of the abnormality Erythrocytes from patients in remission were agglutinable in anti human globulin serum though all evidence of accelerated hemolysis had subsided This suggested that the agglutinability of erythrocytes in the various mediums could be the result rather than the cause of the disease and that splenectomy produced a remission by removal of the principal site of destruction of abnormal cells On the other hand it seemed that a quantitative relation between the amount of immune body present and the rate of blood destruction might better explain the apparent paradox The authors therefore attempted to devise a method of quantitating the amount of anti body on the red cell so that measurements could be made during active and quiescent phases of the disease

Observations on 11 patients with acquired hemolytic anemia showed sensitization of erythrocytes by an antibody

PERNICIOUS AND OTHER NUTRITIONAL MACROCYTIC ANEMIAS

This title is intended to include instances of pernicious and related macrocytic anemias defined by their response to purified liver extract and to vitamin B Other macrocytic anemias fail to react to these agents but *do respond to crude orally administered liver extract or to pteroylglutamic* acid Recently evidence has been put forward to suggest that the megaloblastic anemia of infancy may be due to a combined deficiency of pteroyl glutamic and ascorbic acid It is possible that the so called citrovorum factor which may be the biologically active form of pteroylglutamic acid requires ascorbic acid for its formation in the body —Ed

Hemopoietic Activity in Pernicious Anemia of Beef Muscle Extract Containing Food (Extrinsic) Factor on Intravenous Injection without Contact with Gastric (Intrinsic) Factor Previous observations had shown that 200 Gm beef muscle is hemopoietically active in addisonian pernicious anemia when 150 ml normal human gastric juice is given by mouth simultaneously If an acid mixture of beef muscle and gastric juice is incubated 12 hours and then neutralized it also is active On the other hand if the incubated mixture is heated to 100 C for five minutes its hemopoietic activity as determined by oral administration is destroyed whereas that of whole liver or liver extract is not detectably affected by such a procedure From this it was assumed that the thermostable *anti pernicious anemia principle of liver was not formed by* the incubation procedure in vitro and that heat merely destroyed a thermolabile factor in gastric juice

If a beef muscle and gastric juice mixture is given at an acid pH (1 8 3 5) after incubation no hemopoietic effect appears whereas if treated with alkali to give pH of 5 7 it is active This suggested that a preliminary chemical interaction occurred between the so called extrinsic factor of beef muscle and the intrinsic factor of normal human gastric juice at or about neutrality within the intestinal tract

Because of this evidence the increased hemopoietic activity in pernicious anemia of liver and of relatively crude liver extracts when given orally with human gastric juice was originally assumed to indicate the presence of extrinsic factor as well as of the anti pernicious anemia principle However it was later shown that even refined liver extracts and pure

mission in both was associated with decrease in amount of adsorbed immune body However in one patient antibody production returned without immediate recurrence of hemolytic anemia This inconsistency is not understood

That definite and sustained leukopenia with neutropenia and thrombocytopenia occurred in several patients with hemolytic disease due to an immune body agent raises questions as to etiology of classic thrombocytopenic purpura and splenic

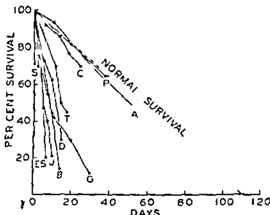


Fig 72—S l t m of t fused ells n p t ts w th h molyt nd pat nts w th oth r type of h m lyt d sease P t ts *S ES J B* 7 a 1 *G* sh wed s t zat n of e ythrocyte p t ts *C P* d *A* h d ong t l h lyt c j und ce Med ter an a an mia d p o ysm l nocturn l h moglob (Co te y of E ns R S nd D n R T Blo d 4 1196 1 13 N embe 1949)

neutropenia Some patients observed seem to have transition forms between acquired hemolytic anemia and thrombocytopenic purpura Sensitized platelets may be susceptible to agglutination and phagocytosis and the presence of an antiplatelet antibody in the circulation may damage the cytoplasm of the megakaryocyte so as to inhibit the formation of platelets

[This last is interesting in view of the demonstration by Ackroyd (this YEAR BOOK p 442) of platelet agglutination in the plasma of patients exhibiting thrombocytopenic purpura due to sensitization to sedormid®—Ed]

sorption of glucose l tyrosine or digestion products of casein

[Subsequent observations continue to point to vitamin B only as the material potentiated by gastric juice —Ed]

Antianemia Activity of Fecal Extract from Pernicious Anemia Patient Microbiologic assay has shown that patients with untreated pernicious anemia excrete in feces substances which act as growth factors for Lactobacillus lactis Dorner the organism used for assay of vitamin B_{12} Four substances in liver have been found to be active for this organism and one of these thymidine failed to induce a remission in a case of pernicious anemia S T E Callender B J Mallett G H Spray and G E Shaw[1] therefore attempted to find whether the substances active for L lactis Dorner in feces of untreated pernicious anemia patients were also effective against the anemia

When 5 ml of a properly prepared extract of feces was injected intramuscularly daily for five days into a patient with untreated pernicious anemia an optimal reticulocyte response and rise in hemoglobin occurred and the marrow previously megaloblastic changed to normoblastic Chromatography of the extract suggested that the antipernicious activity was due to vitamin B_{12} itself

[Bethell has made similar observations Because Cirdwood ha hown that the daily fecal output contains about 0 5 mg of pteroylglutamic acid unless known to be ab ent it may have been involved in these results —Ed]

Decrease of Renninogenuria in Pernicious Anemia and Its Diagnostic Value in Liver Treated Patients was studied by Ole Sylvest Externally secreting glands lose some of their secretion into the blood stream and this secretion is excreted in the urine When such glands become acutely inflamed they often become leaky and larger quantities of secretion pass into the blood and thus into the urine (e g the diastasuria in parotitis and pancreatitis) Conversely it i to be expected that when the e glands are atrophied the secretion will be re duced In atrophy of the pepsin and rennin producing glands in the gastric mucosa excretion of pepsin and rennin in the urine must therefore be supposed to decrease or cease

Atrophy of the gastric glands occurs in pernicious anemia Histologic changes in the stomach are most pronounced in the

(1) La t 2 57 J ly 9 1949
( ) Act m d S d a 133 346 349 1949

vitamin B_1 derived from liver when given by mouth were potentiated in their hemopoietic effect by gastric juice

Observations reported here by Frank H Gardner John W Harris Robert F Schilling and William B Castle[9] (Boston) concern questions obviously raised by these findings Can extrinsic factor alone (beef muscle) act directly as the anti *pernicious anemia principle i e* is a *suitable preparation of* beef muscle such as vitamin B_1 hemopoietically effective in pernicious anemia on parenteral administration without contact with gastric juice? Is the hemopoietic potentiating action of intrinsic factor specific only for vitamin B_1 and chemically similar substances in beef muscle and in other foods or does intrinsic factor also facilitate nonspecific absorption or otherwise enhance hemopoietic action of other substances?

Observations were made during successive periods of 10 or more days on seven patients with addisonian pernicious anemia A 70 per cent alcohol extract of beef muscle was the source of food (extrinsic) factor When 10 ml extract was given daily by mouth to these patients a detectable reticulocyte response appeared in only one instance When the extract was given with normal human gastric juice to four patients reticulocyte responses appeared in all when the material was subsequently given *intravenously* without gastric juice to three of these patients another reticulocyte response appeared indicating greater hemopoietic activity

In two patients it was shown that hemopoietic effect of 10 ml beef muscle extract on daily intravenous injection was less than that of daily intramuscular injection of 1 μg crystalline vitamin B_{12} Microbial assays indicated that 10 ml beef muscle extract contained 0 37 0 9 μg vitamin B_1 activity

Judging from previous observations on the potentiation of crystalline vitamin B_1 by normal human gastric juice *the* hemopoietic activity of the beef muscle extract when given orally with gastric juice appeared surprisingly great However only this fact suggested that substances in the meat extract other than vitamin B_1 were susceptible of potentiation by normal human gastric juice on oral administration in pernicious anemia No evidence was obtained for a nonspecific effect of gastric (intrinsic) factor in increasing hemopoietic action of pteroy*lglutamic acid or in promoting* intestinal ab

(9) J Lab & Cl Med 34 150 1511 N mb 1949

sore tongue indigestion and weight loss occurred and anemia recurred She complained of abdominal discomfort and distention and of paresthesia in the hands and feet Some months later she was hospitalized. Slight clubbing of fingers edema of legs and glossitis were present There was a swelling apparently composed of firm coils of bowel in the center of the abdomen and peristalsis was visible and noisy Blood study showed hemoglobin 9 4 Gm erythrocytes 2 630 000 color index 1.2 reticulocytes 1 6 per cent and leukocytes 3,200 Sternal puncture revealed an active marrow with both normo- and megaloblastic hemopoiesis There were 12 per cent megaloblasts and 21 per cent normoblasts in the film. A fractional test meal revealed free hydrochloric acid and barium meal study evidence of relative small bowel obstruction with hypermotility Plasma protein was 4 17 Gm per cent.

Treatment consisted of a low fat high protein diet with yeast and proteolyzed liver extract by mouth Plasma protein rose to 6 1 Gm per cent and edema diminished. As a preliminary to operation transfusion of 2 pt blood was given The previous anastomosis was identified 1 in above the ileocecal valve The excluded coil of bowel which was about 2 ft long contained several strictures and the intervening musculature was greatly dilated and hypertrophied The mesentery was thickened as in regional ileitis but the bowel wall was not so rough and appeared whiter than in this disease The excluded loop was resected and side to side anastomosis performed

Recovery was good Liver extract was administered parenterally and despite relapse of anemia once after therapy was discontinued because of sensitization and again after an emotional upset four years after surgery the patient was symptom free and the red cell count had been maintained

[In view of the work of Janet Watson suggesting intestinal bacteria presumably in the colon may compete for available vitamin B_{12}, it seems possible that a small intestinal loop could greatly enhance this competition. —Ed]

Pernicious Anemia and Related Anemias Treated with Vitamin B_{12} Edgar Jones William J Darby and John R Totter[4] believe that vitamin B_{12} should be used in daily doses of 3 μg during the first six weeks of treatment of pernicious anemia and thereafter in daily doses of 1 μg In some patients other factors may be necessary to obtain maximal erythrocyte levels These conclusions are based on personal experience with eight patients and the reported experiences of others

Reticulocyte count was an unreliable quantitative criterion of the adequacy of therapy Often amounts of vitamin B_{12} or liver extract sufficient to produce maximal reticulocyte response failed to produce red cell regeneration

Vitamin B_{12} pteroylglutamic acid and liver extract each

(4) Blood 4 827 844 J ly 1949

hydrochloric acid and pepsin producing area of fundus glands

With a method previously described by the author the renninogen in the urine of 25 normal persons 30 with pernicious anemia and 9 with another kind of gastric achlorhydria was determined Those with pernicious anemia showed no values above 0 3 rennin units/10 ml urine In the normal group values for persons aged 17-46 ranged from 0 6 to 2 8 rennin units and for those aged 63 77 from 0 1 to 1 5 units Histamine administration caused no consistent increase in urine rennin concentration in normal persons

If values above 0 3 rennin units are found in 10 ml of morning urine it is likely that the patient does not have pernicious anemia

Clinical Association of Macrocytic Anemia with Intestinal Stricture and Anastomosis D G Cameron G M Watson and L J Witts[3] (Radcliffe Infirm Oxford England) review 60 cases from the literature and report 1 case Peripheral blood smears were identical with those of patients with addisonian pernicious anemia and bone marrow studies revealed some degree of megaloblastic change Gastric analysis however often showed free acid Steatorrhea was not commonly found and it seems unlikely that resection was an important factor because in no case was more than 60 cm of intestine removed The cause of anemia in these patients is not understood but macrocytic anemia has occurred in rats after blind loops of small intestine were produced surgically It may be that toxic compounds are formed in such loops which interfere with erythropoiesis In some rats anemia responded to injections of liver extract Liver therapy was used in 27 of the 61 patients with success in 22 In several surgical correction of the intestinal abnormality led to cure of anemia

Woman 42 whose mother was known to have pernicious anemia presented symptoms of subacute intestinal obstruction Relief from abdominal symptoms followed anastomosis of adjacent loops of ileum A year later she again became ill and was found to have severe hyperchromic anemia with a hemoglobin value of 5 9 Gm per cent and an erythrocyte count of 1 690 000 Blood film showed macrocytosis anisocytosis and poikilocytosis Treatment with an oral liver preparation was effective

Four years later she was unable to obtain oral liver extract and was given a preparation intramuscularly Despite intensive therapy

(3) Bl od 4 793 802 J ly 1949

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(4) Blood 4 827 844 July 1949

reduced the fecal urobilinogen output possibly by decreasing urobilinogen formation by promoting formation of less fragile red cells or by decreasing urobilinogen formation in some nonhemopoietic tissue

Because no change in urinary excretion of pteroylglutamate or of porphyrin was detected in patients given vitamin B_1 it is inferred that the effect of this vitamin does not depend on great release of pteroylglutamic acid

The authors also gave vitamin B_{12} to one patient with nutritional macrocytic anemia one with sprue and one with anemia associated with intestinal lipodystrophy Erythropoietic response was satisfactory in all In two patients mild neurologic involvement was relieved by vitamin B_1 alone

Vitamin B_1 is regarded as the third chemically distinct substance demonstrated to possess hemopoietic activity pteroylglutamic acid and thymine being the other two

[In our experience it is certainly not necessary to give daily doses of purified liver extract or of vitamin B to promote excellent hematologic and clinical remissions After the first sure signs of response weekly injections will suffice for the next six weeks when blood regeneration will usually be reasonably complete Thereafter we give injections once a month at the rate of 1 U S P unit a day —Ed]

Variable Response to Vitamin B_1 of Megaloblastic Anemia of Infancy is reported by Calvin W Woodruff Howard W Ripy J Cyril Peterson and William J Darby[5] (Vanderbilt Univ) The term megaloblastic anemia has been used to designate normocytic or macrocytic anemia in infancy and childhood characterized by megaloblastic arrest of bone marrow The disease responds to liver extract or to pteroylglutamic acid Isolation from liver of another hemopoietic substance vitamin B_1 and demonstration of its effectiveness in pernicious anemia provides an additional tool for study of megaloblastic anemia Available information indicates that 1 μg B_1 possesses hemopoietic activity in pernicious anemia of approximately 1 U S P unit of purified liver extract A single dose of 25 μg is usually followed by a maximal reticulocytosis in pernicious anemia

The authors report excellent response in two patients with megaloblastic anemia of infancy treated with vitamin B_1 a third patient showed no hematologic response but later responded well to folic acid Hematologic response of the first

(5) P d t 4 7 3 729 De mb 1949

two patients to vitamin B_{12} was in all respects comparable with that obtained with folic acid or liver extracts

Experience with these three patients suggests that the megaloblastic anemia of infancy may be not a single entity but rather a syndrome some cases of which may respond to one of the newer hemopoietic vitamins while other cases respond to another

[Agreed The first two patients probably had a limited intake of vitamin B_{12} The third judging from recent observations by Luhby and by May had a deficient intake of folic acid or one made inadequate by a controlling deficiency of ascorbic acid —Ed]

Effect of Animal Protein Factor Concentrate on Persons with Macrocytic Anemia of Pernicious Anemia, of Nutritional Macrocytic Anemia and of Sprue, and on Persons with Nutritional Glossitis For 15 years investigators have been working intensively on an illusive vitamin or a complex of closely related factors found in association with proteins of animal origin For a number of years there has been evidence that soya bean meal was not adequate as the only source of protein in poultry feeds Hatchability of eggs produced by hens fed these diets was low whereas this defect could be remedied by feeding meat scraps With isolation of vitamin B_{12} a long sought for antipernicious anemia factor of liver investigators reported that it possesses animal protein factor activity for the chick and concluded that it is identical with or closely related to the animal protein factor from other sources

Tom D Spies Guillermo Garcia Lopez Fernando Milanes Robert E Stone Ruben Lopez Toca Tomas Aramburu and Sam Kartus[6] therefore studied the effectiveness of an animal protein factor concentrate produced by micro organisms (supplied by Dr T H Jukes of Lederle Laboratories Inc) in five cases of pernicious anemia four of nutritional macrocytic anemia three of nutritional glossitis and three of tropical sprue After baseline determinations were completed animal protein factor concentrate was injected in amounts ranging from a total of 5 cc in 23 days to 5 cc daily for 14 days

Intramuscular injection of animal protein factor concentrate in pernicious anemia nutritional macrocytic anemia and tropical sprue was followed by a positive hematologic response in each case Parenteral administration in nutritional glossitis unassociated with anemia led to disappearance of

(6) Blood 4 819 8 6 J ly 1949

redness and soreness of the tongue The limited amount of clinical biologic and chemical evidence available in studying animal protein factor might suggest that this substance is identical with vitamin B_1 More complete evaluation is needed

[Similar results in pernicious anemia have been reported by Stokstad and his associates —Ed]

Pteroyl Polyglutamic Acids in Treatment of Pernicious Anemia The remarkable therapeutic and hematologic results obtained with folic acid in treatment of pernicious anemia naturally suggested that folic acid deficiency played a part in etiology of this disease consequently some workers suggested that patients with pernicious anemia were able to utilize only the parent folic acid and not the pteroyl polyglutamates from which it is normally formed Because of conflicting reports as to whether patients with pernicious anemia can utilize folic acid conjugates and the bearing of these results on etiology of pernicious anemia John F Wilkinson and Martin C G Israels[7] (Univ of Manchester) extended their studies using two synthetic folic acid conjugates pteroyl tri γ glutamic acid (teropterin®) and pteroyl di α glutamic acid (diopterin®)

Thirteen patients with pernicious anemia were treated Eight were given teropterin® alone via intravenous intramuscular and oral routes All had normal responses with reticulocytosis and subsequent increases of red cells and hemoglobin Three were given diopterin® alone intravenously and intramuscularly Doses available were minimal but all three had reticulocyte responses and reasonable increases of red cells and hemoglobin Two patients were given diopterin® and then teropterin ® one responded poorly to diopterin® but well to teropterin ® and the other responded satisfactorily to both

The authors conclude that patients with pernicious anemia can hydrolyze and utilize folic acid conjugates (pteroyl poly glutamic acids) whether of a naturally occurring γ amino type like teropterin ® or an α amino type like diopterin ® which does not occur in nature There is thus no reason to suppose that in pernicious anemia there is a failure to release free folic acid from its conjugated form

[Since it is known that the synthetic mono glutamic acid commonly employed under the name of folic acid or pteroylglutamic acid is effective in pernicious anemia in 0 5 1 0 mg amount daily it would have been

(7) La t 2 689 691 Oct. 15 1949

more meaningful had these observations not been conducted with such huge doses as 100 mg at a single injection —Ed]

Studies in Pernicious Anemia Patients Treated with Liver Extract and Folic Acid Antagonists Leo M Meyer Norton D Ritz Anthony Caccese Julius Rutzky Arthur Sawitsky and George Bock[8] (New York City) found that folic acid antagonists *do counteract the erythropoietic effect of liver extract* in patients with pernicious anemia The dose of folic acid antagonist necessary to prevent reticulocytosis and increase in hemoglobin and red cells varied in different patients In one patient 40 mg met fol B (methyl pteroic acid) daily had only a partial effect whereas 200 mg daily resulted in no reticulocyte response and a stationary blood picture for one month After discontinuance of the drug further administration of liver extract was followed by slow rise in hemoglobin and red cells but no reticulocytosis Another patient also had a weak reticulocyte response with an actual fall in hemoglobin and red cells necessitating transfusion when given 40 mg of antagonist daily and 10 units of liver extract Adequate liver therapy and 60 mg of antagonist daily were followed by no reticulocytes or change in peripheral blood count After the antagonist was discontinued and repeated liver extract injections were given there was a slow rise in red cells and hemoglobin but no reticulocyte response was ever evoked A third patient had a similar course After administration of 20 units of liver extract there was complete absence of reticulocyte response and fall in hemoglobin and red cells with only 40 mg of antagonist for four days Injection of 10 units of liver extract produced no change in hemoglobin red cells or reticulocytes Administration of 10 units of liver extract on each of two successive days one week later resulted in a slow increase in hemoglobin and red cells and a very poor reticulocyte response A fourth patient came under observation during a satisfactory reticulocytosis Administration of 200 mg met fol B for 16 days had no apparent effect on reticulocytes but hemoglobin and red cell count remained practically unchanged After the drug was discontinued for 15 days blood count rose slowly The fifth patient was treated with an fol R (pteroylaspartic acid) a less potent folic acid antagonist than met fol B and sulfadiazine was

(8) Am J M S 218 197 03 August 1949

administered to prevent liberation of folic acid in the small intestine Although satisfactory reticulocyte response occurred after 10 units of liver extract no change in hemoglobin and red cells took place In three of these patients pronounced megaloblastosis followed treatment with folic acid antagonists even though they received adequate liver therapy All patients uniformly appeared ill and complained of weakness fatigue and somnolence while receiving either antagonist Apparently the drug had a continued effect because after discontinuance patients felt badly had no reticulocyte reactions and no clinical improvements were noted

An additional patient with pernicious anemia in relapse was treated with 200 mg met fol B daily for 14 days but was given 10 and 15 γ vitamin B_1 on the 3d and 11th days and 5 mg a methopterin (4 amino 10 methyl pteroylglutamic acid) intramuscularly No clinical remission or reticulocyte response occurred hemoglobin red and white cell counts did not rise and sternal aspirations revealed megaloblastosis of 11 23 per cent on four occasions

It is concluded that lack of hematologic response in patients with pernicious anemia in relapse treated with adequate doses of liver extract and a folic acid antagonist suggests that pteroylglutamic acid is necessary for production of red blood cells

Idiopathic Steatorrhea (Nontropical Sprue) with Megaloblastic Anemia Liver treatment for tropical and nontropical steatorrhea with macrocytic anemia has been recommended for many years though the response is unpredictable A new line of approach was provided by reports on the effect of folic acid in the West Indian form of tropical sprue which tated that there was remission of megaloblastic anemia and relief from such symptoms as sore tongue anorexia and passage of bulky fatty stools However the number of adequately studied patients is small

M C G Israels and J Sharp[9] (Manchester) therefore report on five patients who had megaloblastic anemia refractory to liver treatment Three of them were also refractory to vitamin B_1 All responded both clinically and hematologically to folic acid

(9) La cet 1 752 756 Ap 22 1950

In these patients the disorder was characterized by pro gressive and often severe anemia infantilism mild finger clubbing and skin rashes of a deficiency type megaloblastic change in marrow usually free HCl in gastric juice and defec tive absorption of fat from the bowel Defective fat absorption may be difficult to detect unless specially looked for If missed diagnosis is likely to be refractory megaloblastic anemia None of these patients was known to have steatorrhea at onset of anemia and in two there were few symptoms to sug gest the diagnosis One patient was originally thought to have idiopathic refractory megaloblastic anemia it responded sat isfactorily to folic acid A year later the patient relapsed and for the first time had fatty bulky stools with fat absorption of only 59 per cent Diagnosis was changed to idiopathic steatorrhea In another patient original diagnosis was achres tic anemia and it was five years before fatty diarrhea dis closed the true diagnosis A 12 day test is essential for accu rate assessment of quantitative changes in fat absorption and if correct diagnosis is to be reached at an early stage

There is now sufficient evidence that there are some pa tients with megaloblastic anemia whose blood picture re sponds well to liver extracts vitamin B_{12} and folic acids and that a second group responds to folic acids but not to paren teral liver extracts or to vitamin B_{12} Addisonian pernicious anemia and nutritional macrocytic anemia as seen in America and the West Indies are in the first group the second group comprises tropical and nontropical sprue pernicious anemia of pregnancy and possibly most patients with nutritional megaloblastic anemia in other parts of the world The authors stress that if there are megaloblastic marrow and free acid in gastric juice the next step irrespective of gross appearance of stools or normal values for fat content of a single fecal specimen should be a fat balance test Only in this way can the few patients be detected for whom folic acid is the treat ment of choice

[Even simpler is to proceed with carefully controlled administration of folic acid with several reticulocyte counts during the first 10 days of therapy —Ed]

Allergic Reactions with Parenteral Liver Therapy and Vitamin B_{12} Bengt Noren[1] (Univ Hosp Upsala) studied

(1) Act med S d 137 48 65 1950

130 patients with pernicious anemia treated with liver parenterally 24 (18 per cent) of whom had allergic reactions Since six had been known previously to be highly sensitive to injectable liver extracts and had therefore been specially chosen for this study 18 per cent may be an exaggeration of the actual number of allergic patients Thirty seven patients had positive skin reaction to one or more commercially prepared liver extracts given intracutaneously and 23 of these showed clinical allergy with manifest symptoms after therapeutic doses of liver extracts The other 14 were classified as latently allergic. One patient with manifest allergic symptoms after liver injections gave negative skin reactions to all extracts used Study of the antigenic properties of liver extracts revealed that the organ specific type of allergy was more common than the species specific (27 and 10 respectively)

Skin tests with chemically pure vitamin B_1 were performed on nine patients all of whom had strongly positive skin reactions to several commercial liver extracts The original solution contained 0 025 mg /ml This was diluted 1 10 and 0 05 ml was injected intracutaneously If the full therapeutic dose of pure vitamin B_{12} is proved to be about 0 015 mg the injected amount expressed in terms of the necessary active dose was much higher than the injected amount of ordinary liver extract used for testing All patients tested with vitamin B_1 showed negative reactions This fact seems to indicate that allergic reactions to liver given parenterally are not usually caused by the pure antianemic factor itself

Allergic reactions began most commonly during the first year of liver treatment after three years complications of this type were uncommon A hereditary tendency to allergy (atopic constitution) as revealed by close questioning about a positive family history of allergy did not seem to be of importance for development of allergic reactions to liver given parenterally

Noren believes that skin tests are not absolutely decisive since a positive reaction may indicate clinical or latent allergy but negative reactions make the presence of manifest allergy extremely unlikely Intracutaneous methods of testing appeared to be more sensitive than scratch tests but in cases in which scratch tests produced positive reactions clinical allergy was usually present Checking of cutaneous sensitivity

as a routine method in all cases of pernicious anemia is not necessary but should be reserved for special cases

[In our experience no organ specific allergy to liver extract has been encountered Invariably a change from extract derived from pork to one from beef or vice versa has resulted in complete relief until in some instances sensitivity to the other species developed The confusion on this point in the literature seems to arise from attempts to interpret skin tests —Ed]

HYPOCHROMIC ANEMIA

The following articles are concerned with various aspects of anemias usually but not always secondary to iron deficiency —Ed

Severe Anemia Secondary to Diaphragmatic Hiatus Hernia Report of 20 Cases is presented by Steven O Schwartz (Cook County Hosp) Bleeding from the stomach in these patients resulted in severe iron deficiency anemias There was a paucity of gastrointestinal symptoms but cardiovascular symptoms were prominent Physical examinations revealed no significant abnormalities It is suggested that in patients especially women past middle age with an iron deficiency anemia but without a history of bleeding without localizing symptoms and significant physical changes diaphragmatic hiatus hernia should be ruled out before other diagnoses are entertained

Definitive diagnosis of diaphragmatic hernia is based on x ray studies Small or reducible hernias are likely to escape discovery unless the examiner is alert for such clues as (1) displacement of the lower segment of the esophagus (2) tortuous but not dilated terminal esophageal segment (3) angulated segment (4) undue retardation of the barium stream at the hiatus (5) gastric content level above the esophageal aperture (6) differentiation of what apparently is high hourglass contraction of the stomach with a visible niche at the constriction site and which often is a stomach hernia through the diaphragm with the ulcer merely a complication

In most patients with diaphragmatic hernia bleeding is due to congestion of the mucous membrane and venous enlargement in the walls of the herniated portion of the stomach Ulcers in the herniated portion of the stomach have been

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(2) Ill M J 97 204 210 Ap 1 1950

130 patients with pernicious anemia treated with liver parenterally 24 (18 per cent) of whom had allergic reactions Since six had been known previously to be highly sensitive to injectable liver extracts and had therefore been specially chosen for this study 18 per cent may be an exaggeration of the actual number of allergic patients *Thirty seven patients* had positive skin reaction to one or more commercially prepared liver extracts given intracutaneously and 23 of these showed clinical allergy with manifest symptoms after therapeutic doses of liver extracts The other 14 were classified as latently allergic. One patient with manifest allergic symptoms after liver injections gave negative skin reactions to all extracts used Study of the antigenic properties of liver extracts revealed that the organ specific type of allergy was more common than the species specific (27 and 10 respectively)

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placental transfer and is analogous to increase in iron binding capacity of serum in iron deficient states Elevation in plasma copper would seem to be independent of changes in iron since there was no correlation in time or degree between these two values Additional knowledge concerning metabolism and functions of copper is needed before conclusions can be drawn concerning its significance in various clinical conditions

Intravenous Iron in Hypochromic Anemia Associated with Rheumatoid Arthritis was investigated by R J G Sinclair and J J R Duthie[4] (Edinburgh) Hemoglobin levels were measured on 100 consecutive patients with rheumatoid arthritis on admission and discharge from hospital Average hospital stay was six weeks All patients were on the same basic regime which included full diet and vitamin concentrates with extra proteins if necessary Patients with hemoglobin levels below 80 per cent were given iron orally in the form of fersolate beginning with a dose of 3 gr three times daily and increasing to 6 gr during their stay Hemoglobin levels remained below 80 per cent in 12 per cent of these cases The effect of intravenous iron in the patients who did not respond to oral iron was then investigated A test dose of 50 mg ferrivenin was given to exclude patients unduly sensitive to the drug subsequent treatment was five 200 mg doses daily In 16 of 23 patients a satisfactory rise in hemoglobin followed administration of intravenous iron

Intravenous administration of iron is worth a trial in all patients with hypochromic anemia associated with rheumatoid arthritis who do not respond satisfactorily to iron by mouth With daily doses not exceeding 200 mg toxic effects were insignificant

[It is probably even more important not to give a large total amount of iron because of the possibility of producing hemosiderosis The authors policy of a total of 1 Gm seems sensible It should be appreciated however that no significant rise in hemoglobin values could be expected before two weeks at a relatively high initial level On the other hand the iron injections should not simply be continued until that event occurs for it may never appear in the face of chronic infection —Ed]

Iron Overload (Hemosiderosis) Aggravated by Blood Transfusions is reported by E E Muirhead G Crass F Jones and J M Hill[5] (Dallas Tex) Excessive iron deposits in the body are usually placed in one of two categories (1)

(4) Lancet 2 646 647 Oct 8 1949
(5) Arch Int Med 83 477 501 May 1949

reported They are the result of trauma and are usually in the lower end of the esophagus near its juncture with the stomach Traumatic ulcers result from to and fro action of the stomach in the hernial ring when the hernia is small and from forceful pressure exerted on the large distorted and congested stomach during attacks of vomiting when the hernia is large

Studies on Free Erythrocyte Protoporphyrin, Serum Iron, Serum Iron Binding Capacity and Plasma Copper during Normal Pregnancy were carried out by Jane Fay G E Cartwright and M M Wintrobe[3] (Univ of Utah) to determine the chemical pattern of the blood in the pregnant state Measurements in 86 normal pregnant women revealed a decrease in packed red cell volume in the latter part of pregnancy There was no significant change in free erythrocyte protoporphyrin although a slight elevation of the mean was found during the latter phase of pregnancy A diminution in serum iron was evident during the latter part of pregnancy and at the same time the iron binding capacity of serum increased Plasma copper values increased during the first trimester and remained elevated during pregnancy Normal values were regained during the first two months post partum Plasma copper values were considerably higher in maternal than in placental blood whereas the converse was true for serum iron

Changes noted during pregnancy differ in certain respects from those observed in various types of anemia Serum iron values in pregnancy did not reach the extremely low levels seen in iron deficiency nor was there the pronounced increase in free erythrocyte protoporphyrin seen in iron deficiency anemia The chemical pattern did not correspond to that observed in the anemia of infection in which an increase in erythrocyte protoporphyrin and a decrease in iron binding capacity of serum occurs

Iron binding capacity is increased during the latter half of pregnancy when demand for iron by the fetus is greatest Present observations reveal a close time correlation between decrease in serum iron and increase in iron binding capacity It may be that elevation in iron binding capacity is part of the mechanism for increased iron absorption mobilization and

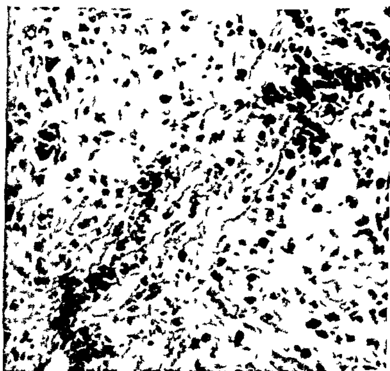
(3) J Clin Investigation 28 487-491 May 1949

tients was compared with that of the same type of tissues from 10 patients who died suddenly and in whom there was no apparent abnormality of these tissues Iron content was much higher in the five anemic patients Of interest was the preponderant concentration of iron in the liver In four cases total amount of liver iron approximated the total amount known to have been given in the transfused blood But a preponderance of iron was also observed elsewhere in the body therefore an additional source of iron must exist Absorption by the intestinal mucosa despite an already existing excess seems the most likely source Figure 73 illustrates a section of liver from one of these patients

The types of anemia in the five patients were acquired hemolytic anemia in two aplastic anemia in two one of whom had a pulmonary fungus granuloma and the other a tuberculoid granulomatous nephropathy and in one classic pernicious anemia with repeated relapses due to the patient s failure to maintain liver therapy Each of these anemias is known to be associated with increased plasma iron concentration and with some increase in tissue iron content In these instances tissue iron content however was greatly increased and was of the magnitude ascribed to hemochromatosis In the lungs interstitial fibrosis was prominent accompanied by pneumonitis Excessive liver damage had occurred in three to five cases Kidneys contained iron casts and displayed clinical evidence of functional impairment Hepatitis occurred in three patients and the likelihood of homologous serum hepatitis cannot be excluded Moderate renal insufficiency might be blamed in part on severity of the anemia Explanations other than iron deposits for the observed findings are therefore possible nevertheless it seems that excessive intracellular iron deposits should have adverse functional as well as morphologic implications

Eventual outcome for patients with refractory anemia does not appear good Development of isoimmunization of milder types leads to a shorter and shorter span for infused erythrocyte Greater frequency of transfusions means more iron is being deposited throughout the body The large iron deposits in reticuloendothelial elements may act to produce effects of a reticuloendothelial block thus lowering resistance to infectious agents

Hemosiderosis is characterized by widespread iron deposition associated with prolonged hemolysis or following repeated experimental *injection of hemoglobin solution intravenously* (2) Hemochromatosis is most often characterized by wide spread iron deposition (hemosiderin pigment) hemofuscin



Fg 73—S t f l b w g d troy d d l p d t l p ton f hep t c l bul d h y m l t of n n p en h m l d K pff c ll (Cou tesy of M h d E E t l A h I t M d 83 477 501 M y 1949)

deposits increased copper content of tissues cirrhosis and hypogonadism pancreatic damages and diabetes mellitus and kin pigmentation These features of hemochromatosis vary in intensity and in frequency of their combination

At autopsy five anemic patients who had required transfu sions over *prolonged periods* had widespread iron deposits in various tissues and parenchymatous tissue damage Iron con centration in liver pancreas kidneys and lungs of these pa

time was anti A agglutinin detected in the infant s serum and the red cells gave a negative Coombs reaction Antibodies in the mother s serum for the five Rh Hr antigens in bloods of type Rh_1Rh_2 could not be demonstrated Up to age 17 months repeated examination showed the defect in hemopoiesis to be confined to failure of red cell formation Repeated transfusions are necessary to maintain normal blood levels

The only causative factor for anemia that can be postulated in this case is the possibly injurious effect on fetal erythropoiesis of the anti A agglutinin elaborated by the mother in an incompatible pregnancy Although the blood disorder at onset of the patient s illness can probably be safely classified as erythroblastosis fetalis relationship of the anti A agglutinin to depression of erythropoietic centers and continuance of the anemia require elucidation It is conceivable that erythropoiesis in the fetus may be impaired by prolonged reaction with an antibody in high titer against its own red cells in the course of an incompatible pregnancy It has been pointed out that the A and B blood agglutinable factors can be demonstrated in the fetus between the second and third month and the possibility of early isoimmunization in the first months of fetal development has been suggested Therefore prolonged exposure of red cells and their precursors during a vulnerable period of fetal life to the anti A agglutinin may be responsible not only for anemia at birth but for its persistence in the neonatal period

To test further the hypothesis that erythropoiesis may become depressed in erythroblastosis fetalis bone marrow was aspirated in several instances of this disease during protracted anemia Individual examinations showed a decreased percentage of nucleated red cells in several cases regardless of whether treatment consisted of subtotal blood replacement or multiple transfusions

Blood and Bone Marrow in Patients with Cirrhosis of Liver were analyzed by Lawrence Berman Arnold R Axelrod Thomas N Horan Samuel D Jacobson Elwood A Sharp and Elmore C VonderHeide[7] (Detroit) on the basis of a review of the literature and their study of 25 patients with diagnoses verified by liver biopsy Complete blood studies with simultaneous aspiration biopsy of sternal marrow obtained

(7) Blood 4 511 5 8 M y 1949

OTHER ANEMIAS

Chronic Congenital Aregenerative Anemia (Pure Red Cell Anemia) Associated with Isoimmunization by Blood Group Factor A Causative factors of aplastic and hypoplastic anemias include chemical and physical agents infection exhaustion of bone marrow and specific blood dyscrasias and malignant tumors with bone marrow replacement When these factors have been eliminated a relatively rare group of idiopathic aplastic anemia remains which has been attributed to congenitally inferior bone marrow Aplastic anemia is a chronic progressive disease characterized by simultaneous depression of the three principal cellular elements in bone marrow and resulting in a peripheral blood picture of profound anemia leukopenia neutropenia and thrombocytopenia Hypoplastic anemia differs from aplastic anemia in that red blood cell formation is impaired with lesser involvement of granulocytes and platelets When failure of hemopoiesis is restricted entirely to erythrocytes without impairment of leukocytes or platelet production the condition has been designated chronic congenital aregenerative anemia or pure red cell anemia Carl H Smith[6] describes a case in which bone marrow failure was confined to erythropoiesis without simultaneous depression of granulocytes or platelets or their precursors

Boy aged 2 months born three weeks prematurely was hospitalized because of progressive anemia Jaundice developed at age 4 days and did not disappear until the third to fourth week The mother had not been pregnant before and there was no history of hereditary blood disorder On admission there was no jaundice heart and lungs were normal and spleen and liver edge were palpable at the costal margin There were no petechiae or other manifestations of bleeding into the skin Hemoglobin level was 9 5 Gm red cell count 3 500 000 white cell count 13 000 with normal differential count packed red cell volume 24 per cent platelets 290 000 reticulocyte 0 2 per cent bleeding time 3 minutes 35 seconds and clotting time 3 minutes The mother s blood group was O Rh positive and that of the infant and father A Rh positive Clinical course and hematologic features appeared similar to those of mild erythroblastosis fetalis perhaps due to isoimmunization of the mother by the offspring Tests of the infant s saliva showed him to be a nonsecretor The mother s anti A serum titer reached a maximum of 1 128 000 At no

(6) Blood 4 697 05 J 1949

megaloblastic anemias and the macrocytic anemia of cirrhosis as peripheral blood study does not provide evidence of the type of erythropoiesis in marrow

Combined study of peripheral blood and sternal bone marrow may lead the clinician to serious consideration of cirrhosis of the liver Macrocytosis or macrocytic anemia without hypochromasia plus lymphopenia and thrombocytopenia with normal or increased marrow cellularity and normal or increased erythrocytogenesis and megakaryocytogenesis constitutes a hematologic picture which points strongly to cirrhosis of the liver When anemia is absent and the other signs are present the probability of cirrhosis is even greater

The authors conclude that combined blood and sternal marrow study is useful in establishing diagnosis of cirrhosis of the liver in patients in whom other diseases have obscured its manifestations or in whom historical evidence is absent so that clinical diagnosis is difficult

[The many points distinguishing this anemia from pernicious anemia which it may superficially resemble should be noted —Ed]

Blood and Bone Marrow Studies in Renal Disease Irwin R Callen and Louis R Limarzi[8] (Univ of Illinois) studied peripheral blood and bone marrow in 102 patients with nephritis related diseases and hypertension In 44 patients with renal disease of sufficient severity to produce azotemia degree of anemia definitely increased as nonprotein nitrogen rose Abnormalities in other blood values such as chloride CO_2 combining power glucose and albumin and globulin could not be correlated with degree of anemia nor could the degree of anemia be correlated with level of nitrogenous waste products in the blood Review of these patients histories failed to show that albuminuria or a deficient protein diet had any effect on the anemias Hematuria was seen in many patients without anemia and in some with anemia There was no correlation between hematuria and anemia Of the 44 patients with anemia and azotemia 81 per cent had a normocytic normochromic anemia Peripheral blood smears revealed no significant abnormalities

This study has shown that anemia is rarely present in cases of renal disease unless there is an associated elevation of nitrogenous waste products in blood It is however generally

(8) Am J Cl Path 20 3 23 January 1950

within 1/2 24 hours before the liver specimen was removed were carried out on all patients

Principal blood findings were macrocytic or normocytic anemia with normal or elevated mean corpuscular hemoglobin values lymphopenia and thrombocytopenia in most cases Bleeding was not an essential factor in production of anemia in cirrhosis and severity of anemia or macrocytosis did not appear to be related to severity of the liver lesion

A consistent change in bone marrow was extension of the marrow organ so that active hemopoiesis was found in the shafts of long bones Regardless of the presence or absence of bleeding or anemia the sternal marrow was usually of normal or increased cellularity with normal or increased erythrocytogenesis and megakaryocytogenesis Hypocellularity of the marrow was unusual even in patients with advanced liver lesions Macronormoblastic erythropoiesis was seen in patients with macrocytic anemia but megaloblastic erythropoiesis did not result from cirrhosis of the liver

Presence of peripheral cytopenias (anemia and thrombocytopenia) despite normal or increased formation of erythroblasts and megakaryocytes in the marrow was suggestive of hypersplenism in patients with hepatic cirrhosis In patients with chronic hemorrhage blood and bone marrow pictures were those of iron deficiency anemia although other changes such as lymphopenia and thrombocytopenia tended to persist

Changes described cannot be considered pathognomonic of cirrhosis even though they appear to be characteristic of the disease On the other hand it is not justifiable to consider complete blood and bone marrow studies as valueless and without diagnostic importance in cirrhosis In patients known to have the disease appearance of microcytic hypochromic anemia or micronormoblastic marrow indicates chronic blood loss Hypocellular marrow in patients with macrocytic anemia suspected of having cirrhosis is unusual and should point to other or additional factors in the clinical picture Although normocytic or macrocytic anemias are compatible with diagnosis of cirrhosis macrocytic hypochromic anemia as determined by mean corpuscular volume and mean corpuscular hemoglobin values is not typical and should lead to further study of the patient Marrow examination may be of crucial importance in distinguishing between pernicious or other

are most common in cases of splenomegaly in older patients It is now generally accepted that bone marrow rather than the spleen or peripheral blood is primarily at fault The chief argument is whether the changes are reactive or neoplastic

John P Wyatt and Sheldon C Sommers[9] (Boston) studied 30 cases to find clues to the origin morphology and nature of this clinicopathologic montage Twenty autopsies were per



F g 74 (l ft) —V rt t ı m w My l l l g l p t n f t l w th p om t m t l ne S k g d t f m w tt t V l h l p m t H m t yl d ta R l l f m × 50
F g 75 (ght) —St l m w bt d t t p y n th se Ch t t p t f rm l t l h w g p om t f tw k bo p tt Ph ph t g t d h n t yl ta R l d f m × 5)
(C rt y f Wy tt J P d S mm S C Blood 5 3 9 347 Ap l 1950)

formed Salient observations were as follows Necrosis of partly matured erythroid and myeloid bone marrow cells appeared to be the fundamental primary lesion Reactive overgrowth of surviving usually more immature cells followed Extramedullary hemopoiesis identical with that in other diseases developed Integrity and eventual overgrowth of reticular and stromal tissues were uniformly visible in marrow and sites of myeloid metaplasia Hemopoietic cells occasionally underwent violent hyperplasia but the invasive property

(9) Blood 5 3 9 347 Ap 1 1950

accepted that a mild or moderate anemia is present in patients with chronic glomerulonephritis who have impaired kidney function but no azotemia, the implications being that dis turbed kidney function is a factor in production of the anemia This is not in keeping with results in this group Of 22 pa tients having chronic glomerulonephritis without azotemia (azotemia being defined as a blood nonprotein nitrogen level above 40 mg per cent), 10 had mild anemia There was only one instance of anemia in a patient with chronic nephritis who had no elevation of blood nitrogen values when first stud ied or during three years observation It seems safe to say that anemia is not related to proteinuria is not present in nephrosis without azotemia and is not related to damaged kid ney function per se

Normal cellularity or hypercellularity of bone marrow was observed in most patients with nephritis irrespective of its stage In at least 80 per cent of those with azotemia bone marrow was hypercellular mainly myeloid and megakaryo cytic cells being involved Erythropoiesis was normal Only after nonprotein nitrogen reached 150 mg or more did bone marrow show any quantitative evidence of a moderate hypo plasia All bone marrow elements showed some hypoplasia when nonprotein nitrogen rose above 150 mg but erythroid tissue was selectively more affected than other cells Aplastic normoblastic tissue was never observed in these marrows

Discrepancy between anemia in peripheral blood and the apparent adequacy of erythroid tissue in bone marrow in many cases of chronic glomerulonephritis is difficult to ex plain Apparently the mechanism regulating delivery of cells to the blood stream is at fault rather than the maturation of cells This mechanism is a selective one since there is no inter ference with leukopoiesis and megakaryopoiesis The authors emphasize that a cellular bone marrow in chronic glomerulo nephritis is not in itself evidence of hemopoietic activity nor does it have prognostic significance

Chronic Marrow Failure Myelosclerosis and Extramedul lary Hematopoiesis When a case was reported 70 years ago of generalized osteosclerosis with striking hepatosplenome galy anemia hyperplastic lymph nodes and extreme leukocy tosis a controversy began over the nature of this condition which still continues Such clinical pictures are infre uent and

stromal cells and clinical abnormalities develop because of inadequate organ function progressing to organ failure and death In chronic marrow failure five major etiologic groups have been identified extrinsic toxic agents liver dysfunction endocrine disease chronic hemorrhage or hemolysis and cardiovascular disease

The authors developed a working hypothesis of the pathogenesis of chronic marrow failure and myelosclerosis Benzene and related aromatic compounds are metabolized by oxidation to phenol catechol and hydroquinone which normally are rapidly conjugated in the liver to sulfates and glucuronates and excreted in urine Adrenal cortical and estrogenic steroids which possess phenolic or quinone groups are similarly conjugated and excreted by the liver in bile and urine These substances are toxic to the lipoid containing partly mature hemopoietic cells Studies of liver conjugation have shown that coenzyme I is necessary for inactivation of estrogenic phenolic compounds In chronic marrow failure pellagra hemochromatosis and copper poisoning suspicion has been directed toward deficient or inactivated coenzyme I as a basic biochemical lesion Hydroquinone and radiation have been suggested as mitotic poisons which also inhibit other unidentified enzymes

[This is a thoughtful discussion of a complex condition of slow evolution presenting various clinical and pathologic aspects at different stages —Ed]

Hemopoietic Changes during Administration of Chloramphenicol (Chloromycetin®) were observed by Italo F Volini Irving Greenspan Lee Ehrlich James A Gonner Oscar Felsenfeld and Steven O Schwartz[1] (Cook County Hosp) A Negro boy aged 11 with uncomplicated typhoid had a red cell count of 850 000 and 17 per cent (2 6 Gm) hemoglobin four days after discontinuance of therapy He had received a total dose of 53 Gm chloramphenicol orally in 18 days Two other cases were observed almost simultaneously a patient with typhoid complicated by amebiasis had been given 53 Gm chloramphenicol in 19 days and a patient with brucellosis had received 26 Gm in 9 days

There was a precipitous fall in total leukocyte count which occurred by the seventh day in one case and continued

(1) J A M A 14 1333 1335 Ap 29 1950

of leukemic and other neoplastic cells was acquired only exceptionally Histories and laboratory data often incomplete pointed to the etiologic importance of the same agents as those in refractory anemia It is important to differentiate this disease from myelogenous leukemia because the usual therapy for leukemia and splenectomy are contraindicated Splenic hepatic and other extraosseus foci of hemopoietic cells in such patients are attributed to the impossibility of compensatory assumption of blood formation in diseased bone marrow by viscera which had actively formed blood cells during embryonic life It is generally agreed that myelocytes and nucleated red cells in peripheral blood are not certain indicators of myelogenous leukemia

The gross appearance of organs at autopsy will suggest this condition Spleen is 3 30 times larger than normal Fibrosis is at times indicated by resistance to cutting In some cases infarcts are present and there may be dark red or brown spherical demarcated nodules of bulging soft tissue Liver is 1½ 4 times its usual weight but on section does not appear abnormal The marrow may be deep red and succulent displacing the usually intermingled yellow fat and appearing grossly hyperplastic Bones may be uniformly dense gray white and hard with thickened cortices and without well defined marrow spaces

In the literature consulted 129 adequately studied acceptable cases of this morphologic entity were found Natural life span in chronic marrow failure and myelosclerosis usually extends over many years although the patient may not appear for examination until late in its course Search often uncovers evidence of toxic exposure Complete hematologic investigation including bone marrow biopsy (not puncture) is indicated Methods useful in treatment of leukemia and hypersplenism are contraindicated Splenectomy usually shortens the patient s life

Bone marrow has been compared in size with the liver and pathologic analogies may be drawn between myelosclerosis and hepatic cirrhosis Both are morphologic entities without etiologic unity In both diseases various toxic agents deficiencies and injuries cause necrosis of parenchyma followed by reparative hyperplasia of surviving cells Continuance of parenchymal damage leads to overgrowth of the tougher

stromal cells and clinical abnormalities develop because of inadequate organ function progressing to organ failure and death In chronic marrow failure five major etiologic groups have been identified extrinsic toxic agents liver dysfunction endocrine disease chronic hemorrhage or hemolysis and cardiovascular disease

The authors developed a working hypothesis of the pathogenesis of chronic marrow failure and myelosclerosis Benzene and related aromatic compounds are metabolized by oxidation to phenol catechol and hydroquinone which normally are rapidly conjugated in the liver to sulfates and glucuronates and excreted in urine Adrenal cortical and estrogenic steroids which possess phenolic or quinone groups are similarly conjugated and excreted by the liver in bile and urine These substances are toxic to the lipoid containing partly mature hemopoietic cells Studies of liver conjugation have shown that coenzyme I is necessary for inactivation of estrogenic phenolic compounds In chronic marrow failure pellagra hemochromatosis and copper poisoning suspicion has been directed toward deficient or inactivated coenzyme I as a basic biochemical lesion Hydroquinone and radiation have been suggested a mitotic poisons which also inhibit other unidentified enzymes

[This is a thoughtful discussion of a complex condition of slow evolution presenting various clinical and pathologic aspects at different stages —Ed.]

Hemopoietic Changes during Administration of Chloramphenicol (Chloromycetin®) were observed by Italo F Volini Irving Greenspan Lee Ehrlich James A Gonner Oscar Felsenfeld and Steven O Schwartz[1] (Cook County Hosp) A Negro boy aged 11 with uncomplicated typhoid had a red cell count of 850 000 and 17 per cent (2.6 Gm) hemoglobin four days after discontinuance of therapy He had received a total dose of 53 Gm chloramphenicol orally in 18 days Two other cases were observed almost simultaneously a patient with typhoid complicated by amebiasis had been given 53 Gm chloramphenicol in 19 days and a patient with brucellosis had received 26 Gm in 9 days

There was a precipitous fall in total leukocyte count which occurred by the seventh day in one case and continued

(1) J A M A 14 1333 1335 Ap 29 1950

as long as the drug was administered Leukopenia resulted primarily from a decrease in marrow granulocytes due to a maturation arrest without significant alteration in monocytes or lymphocytes Severe anemia occurred in one patient with an erythroid maturation arrest in marrow No significant change occurred in platelet count in the one instance in which this factor was studied Both marrow and blood changes were reversible and an immediate rise in white cell count followed discontinuation of therapy

Although pronounced hematologic changes have been reported to accompany typhoid and no toxic effects have previously been ascribed to orally given chloramphenicol the following evidence strongly suggests the cause and effect relationship between administration of the drug and marrow and blood changes Leukopenia developed after chloramphenicol therapy was started despite definite clinical improvement Absolute and relative granulocyte levels uniformly fell lower than those ordinarily observed in typhoid or brucellosis In every instance marrow showed a relative and absolute granulopenia with maturation arrest An immediate precipitous increase in granulocytes and leukocytes followed discontinuance of chloramphenicol therapy On the basis of erythroid maturation arrest chloramphenicol was probably partly responsible for the decrease in red cells

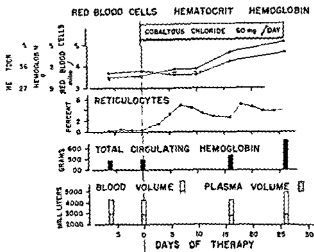
The authors conclude that toxic manifestations of this drug will have to be studied more extensively before it can be considered an absolutely safe therapeutic agent

↓ In the following two articles the effects of cobalt administration in man are discussed Though essential as a trace element in hemopoiesis it does not appear to have useful effects in pharmacologic dosage in the treatment of anemia —Ed

Effect of Oral Therapy with Cobaltous Chloride on Blood of Patients Suffering with Chronic Suppurative Infection Joseph C Robinson G Watson James III and Robert M Kark (Chicago) studied the blood of nine patients aged 18 30 with prolonged suppurative infections treated for 2 11 weeks with 20 60 mg cobaltous chloride daily by mouth The patients had already been hospitalized an average of 28 months for chronic osteomyelitis or chronic soft tissue suppuration They showed no clinical evidence of vitamin or pro

( ) N w E gl d J M d 40 749 753 M y 12 1949

tem deficiencies although all had lost weight Red cell sedi mentation rate was increased plasma iron levels were low and plasma copper levels were increased in all Before treatment red cell counts reticulocyte counts hemoglobin concentra tions hematocrit levels and total circulating hemoglobin were constant and reduced below levels found in bedridden control subjects Total circulating hemoglobin levels were



F g 76—Eff t f baltou hl d blood f y th 19 w th h on t t d t my l t (C t y f R b J C t l h w E gl d J M d 240 749 753 M y 12 1949)

significantly reduced on the average of 26 per cent below values for controls

After treatment reticulocyte responses occurred in all patients as early as the fourth day and continued through out therapy Maximal reticulocyte percentages were usually observed between 6 and 10 days and did not exceed 5 per cent A typical reticulocyte response is shown in Figure 76 In this patient as in the others a steady increase in red cell counts hematocrit levels and total circulating hemoglobin followed the reticulocyte response On the average blood values of all patients reached normal levels after cobalt ther apy There was a significant change in blood volume owing mainly to a 30 per cent increase in circulating red cell mass

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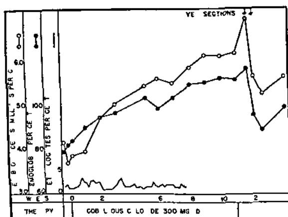
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( ) New E gl d J M d 40 749 753 M y 12 1949

studied the erythropoietic effect of cobalt first in hematologically normal patients then in patients with anemias refractory to recognized forms of treatment A 2 5 per cent aqueous solution of cobaltous chloride was given to 61 patients Generally 4 cc containing 100 mg cobaltous chloride was given orally three times daily after meals

Daily oral administration of 300 mg cobaltous chloride to 17 patients without anemia produced slight reticulocyte re



Fg 77—R lt f b lt dm st t man w th g l d t po d t rth t (Court y f B k L N w E gl d J M d 40 754 61 May 12 1949)

sponses in all within a week All but 1 of the 10 given the drug for over four weeks showed moderate increases in red blood cell hemoglobin and hematocrit values A man 67 with severe generalized osteoporosis and osteoarthritis was given the drug for 11 weeks with striking effects on red cell and hemoglobin levels (Fig 77) After 10 weeks of treatment he complained of poor appetite and sensations of fulness in the head Cobalt administration was stopped a week later and five days thereafter at the height of polycythemia 500 cc blood was removed on two successive days The red cells contained spectrophotometrically normal oxyhemoglobin and survived normally when transfused into another patient

Similar doses were given 32 patients with various types of anemia refractory to other forms of therapy 20 being

the plasma volume changing but slightly Total circulating hemoglobin increased on the average 29 per cent above pre treatment levels In four patients on whom measurements were made before and after treatment plasma iron and cop per levels were not affected by therapy Two patients had slight loss of appetite All showed a dusky skin discoloration especially pronounced below the eyelids It was probably due to the dye T 1824 used for measuring blood volumes but may have been an effect of cobalt No other abnormal signs or symptoms were observed

Hemopoietic responses to cobaltous chloride indicate that the drug produced an active stimulus to erythropoiesis since a distinct reticulocytosis preceded a rise in erythrocyte count Mode of action of cobalt on blood remains a mystery It does not seem possible that cobalt has a spec fic effect on the blood of patients with chronic infections Their anemia is refractory to liver therapy and they require relatively large quantities of cobalt for erythropoiesis to occur Hemopoiesis after mas sive cobalt therapy is more likely due to a nonspecific stimu lus to bone marrow

Erythropoietic Effect of Cobalt in Patients with or without Anemia Cobalt in the form of one of its salts usually co baltous chloride or nitrate has been shown to produce poly cythemia in amphibia birds and mammals Since pioneer observations in 1929 metallic cobalt or its salts have been given to animals and man in efforts to combat anemia pro- duced by disease It has been reported that cobaltous nitrate counteracts the inhibitory effect on erythropoiesis of benzene administration in rabbits and that cobalt administration abolishes anemia or even produces polycythemia in rats with sterile inflammation produced by intramuscular injection of turpentine Only a few results briefly documented have been reported from use of cobalt salts as a stimulus to erythropoie- sis in human disease However almost at the time the present investigation was begun a report in the German literature indicated that oral administration of 500 mg cobaltous chlo ride daily regularly produced reticulocyte responses in normal subjects and thereafter increases in red cell hemoglobin and hematocrit values

Lionel Berk Joseph H Burchenal and William B Castle[3]

(3) N w E gla d J Med. 40 754 761 M y 12 1949

HYPERSPLENISM

The use of this term with its implications has the sanction of several authorities They conceive the existence of hematologic conditions usually associated with splenomegaly to result from an exaggerated function of the spleen For this reason a few articles have been segregated in this section However we doubt that the concept of primary hyperfunction of the spleen can be supported, despite the fact that splenectomy is frequently a useful procedure Rather it appears to us that owing to a variety of causes originating external to the spleen the organ may become secondarily enlarged and its function increased The very number of recognizable causes of secondary splenomegaly associated with anemia leukopenia and thrombocytopenia or sometimes with only one of these suggests this interpretation Thus in congenital hemolytic jaundice the red cell defect is clearly primary and persists after splenectomy With congestive splenomegaly of origin internal or external to the liver or a spleen enlarged by infiltration by Gaucher's cells leukopenia and thrombocytopenia are common In various instances of acquired hemolytic jaundice agglutination of the red cells sometimes augmented by slight lowering of the pH of the serum is observed. If the normal spleen as can easily be shown is able selectively to retain spheroidal red cells it should even more readily sequester red cells that are agglutinated

Even among those convinced of the primary nature of the process both hyperphagocytosis in the spleen and hypofunction on the part of the marrow as a result of undetermined splenic humoral influences are proposed as explanations Consequently there is no general agreement as to the definitive diagnostic criteria of hypersplenism As splenomegaly with anemia leukopenia and thrombocytopenia are common to such diverse conditions as for example refractory anemia with hyperplastic bone marrow aleukemic myelogenous leukemia and disseminated lupus the diagnosis of hypersplenism is possible only in retrospect when splenectomy effects a change toward normal in the blood picture In our limited experience this can happen only when manifest leukemia develops months or even years later In a later section articles on chronic sometimes cyclic agranulocytosis are assembled The varied morphology of the bone marrow and the indifferent effects of splenectomy are to be noted This does not deny the utility of splenectomy in certain patients it only suggests the uncertainty of the concept of hypersplenism as a primary aberration of the spleen —Ed

Problem of Hypersplenism is *summarized* by Roy R Kracke and William H Riser Jr [4] (Birmingham Ala) Functional overactivity of the spleen (hypersplenism) includes a variety of hematologic syndromes with multiple clinical pictures in which the spleen has the capacity to destroy various blood cells Such syndromes *include chronic* and *acute splenic* neutropenia *chronic and* acute splenic panhematopenia of congenital and acquired types familial hemolytic icterus and idiopathic thrombopenic purpura

(4) J A M A 141 315 1139 *Dec 17 1949*

treated over four weeks Two of five with moderate anemia associated with chronic infections one of two with hypochromic anemia associated with inoperable gastric carcinoma and one with familial microcytic (Cooley s trait) anemia showed definite reticulocyte responses and rises in red cell hemoglobin and hematocrit values

Only 3 of 16 patients in the lymphoma group—2 with reticulum cell sarcoma and 1 with chronic lymphatic leukemia—showed even suggestive evidence of ability to maintain higher erythrocyte and hemoglobin levels In none of five patients with refractory anemia and hypercellular bone marrow was erythropoiesis detectably affected One patient with anemia of hepatic cirrhosis showed no response in an adequate trial Two patients with anemia associated with chronic renal failure given the drug for only a few days showed no evidence of a reticulocyte response

From these observations it seems clear that cobaltous chloride increases erythropoiesis in hematologically normal subjects Reticulocyte responses resembled in chronology those resulting from hemorrhage anoxia or iron or liver extract administration under circumstances appropriate to each This observation is seemingly consistent with the possibility that cobalt interferes with transport of oxygen in erythroid cells of the bone marrow because of its ability to form oxygen binding complexes with certain amino acids such as cysteine and histidine If so the agent would be expected to be effective in elevating the hemoglobin level in patients with little or no anemia rather than in those with severe anemia in whom a powerful anoxic stimulus to erythropoiesis presumably already exists

There is little evidence of toxicity of cobalt at least after oral administration other than irritation of the alimentary tract However there is also little probability of benefit in severe types of anemia otherwise unamenable to therapy In mild anemias associated with chronic infections benefit due to a slight increase in hemoglobin may well be offset by loss of appetite due *to the drug Therefore clinical use of* cobalt should be limited to cases of anemia in which other methods of treatment are clearly of no value There is no indication for use of cobalt as an adjuvant to liver or iron therapy

pleted cell values in blood including neutropenia thrombopenia anemia or various combinations of these demonstration of unimpaired bone marrow production and demonstration of splenic overactivity by the epinephrine test The basic problem in hypersplenism is to determine whether or not the spleen is destroying more cells than it should and whether or not the bone marrow is capable of producing the normal number of cells to support the particular patient then the danger of leaving the spleen in the patient can be weighed against the operative risk of removing it Splenectomy is always a serious surgical procedure and should be carried out only by a competent surgeon

Primary Splenic Panhematopenia The term splenic panhematopenia is used to designate a syndrome characterized principally by splenomegaly panhyperplasia of the bone marrow and varying degrees of anemia neutropenia and thrombocytopenia The syndrome is divided into primary splenic panhematopenia on a congenital or familial basis and splenic panhematopenia secondary to some constitutional pathologic process with disturbed splenic physiology The primary type of splenic panhematopenia may occur as a chronic relapsing disease with intermittent episodes of hemoclastic activity or as a relatively acute disease characterized by prostration and rapid depression of the cellular elements of the blood The secondary acquired form of panhematopenia has been observed in Hodgkin s and Gaucher s diseases

Based principally on results of epinephrine tests supravitally stained preparations of freshly excised splenic tissue and histologic appearance of the bone marrow it has been thought that the hematologic alterations in splenic panhematopenia are due to sequestration of erythrocytes leukocytes and thrombocytes in the splenic sinusoids and destruction of these elements by reticuloendothelial macrophages In most cases reported subcutaneous administration of 0 5 1 cc epinephrine produced significant elevation of number of circulating erythrocytes leukocytes and thrombocytes

During the past few years Robert W Heinle and William D Holden[5] (Cleveland) have diagnosed primary splenic panhematopenia in seven instances The patients presented the picture described in primary splenic panhematopenia Neu

(5) S g Gynec & Ob t 89 79 91 J ly 1949

The spleen is the most important organ in the body with respect to cellular destruction Histologic evidence can be seen in the large endothelial cells which show fragments of red and white cells and thrombocytes incorporated in the cytoplasmic structure Furthermore motion pictures of the splenic pulp clearly show the active process of phagocytosis by the ameboid endothelial elements of the spleen Examination of the venous blood supply shows a definite increase of bilirubin in the splenic vein compared with the splenic artery Other evidence of cellular destruction is found in large deposits of hemosiderin the iron containing pigment of disintegrated red cells

In addition to removing cellular elements from blood by phagocytosis and ultimate destruction the spleen is also capable of removing large masses of cells from the vascular system by enlargement and sequestration of the cells in the dilated and engorged organ Therefore it is a reservoir the chief function being to store blood however this function may become perverted and excessive numbers of cells removed from the vascular system resulting in depleted cellular values in peripheral blood This storing of large quantities of cells can be amply demonstrated by the epinephrine test An injection of 0 5 1 cc of 1 1 000 epinephrine solution will cause contraction of the organ and a simultaneous rise in cellular value in peripheral blood

Most circulating blood cells are produced in bone marrow which has a tremendous reserve capacity for producing blood cells The relation of marrow production and splenic destruction may be summarized as follows normal marrow production plus normal splenic destruction produces normal cellular equilibrium impaired production plus normal destruction causes depleted cellular elements normal production plus excessive destruction causes depleted cellular elements The spleen may be hyperfunctional for many years but if cellular destruction is not too great the marrow may be able to maintain normal cellular values Only when marrow decompensation occurs do signs of anemia thrombopenia and neutropenia develop

Diagnostic criteria for hypersplenism include these cardinal features a spleen clinically enlarged the single exception being some cases of essential thrombopenic purpura de

preponderant and their action results in pathologic conditions It has been stated that excessive hemolysis is due either to normal hemolytic agents acting on defective erythrocytes or to exposure of red blood cells of normal resistance to lytic agents in unusual quantity or of unusual activity Whichever occurs the spleen must play an important role since splenectomy has proved life saving in management of certain hemolytic syndromes Evidence seems to accumulate that the macrophages of the spleen are specifically responsible for the abnormal activity They not only dispose of the effete blood cells by engulfing them but also elaborate various enzymes which prepare the blood cells for destruction

George J Scheff and Ahmed J Awny[6] (Ohio State Univ) studied lecithinase activity in 10 pathologic spleens (9 obtained at operation) and 2 normal spleens obtained at autopsy Patients operated on had typical essential thrombocytopenic purpura splenic neutropenia and congenital hemolytic icterus In all of them the spleen was the major factor in the ailment so that the term hypersplenism was applicable to all In all the pathologic spleens increased lecithinase activity was demonstrated by increased formation of lysolecithin in vitro In the two normal spleens this effect was lacking

Mere demonstration that the reticuloendothelial cells of the spleen are numerically increased and functionally hyperactive in producing the enzyme would not be sufficient to explain the whole picture in hypersplenism These cells are widely distributed in the organism and are not restricted to the spleen alone To explain the key position of the spleen in hemolytic processes the authors emphasize that in the spleen circulation is largely cut off from the main blood flow and therefore blood is permitted to stagnate for various lengths of time Complete separation between cells and plasma is also thought to exist In these circumstances not only is the lecithinase activity enhanced in hypersplenism owing to the increased number of macrophages in the spleen but simultaneously the inhibitory effect of plasma is reduced to a minimum In addition a more intimate contact between blood cells retained in meshwork of the pulp and the freshly elaborated lysolecithin can be established This may gradually lead to spherocytosis and to sensitization of the erythrocytes for

(6) Am J Cl Path 19 615 679 July 1949

tropenia anemia and thrombocytopenia occurred in all and varied from mild to severe Splenomegaly was constantly present but variable in degree Purpura was observed depending on degree of thrombocytopenia Oral ulcerations were present in one patient and chronic ulcers on the legs of another both of whom had severe and presumably chronic, neutropenia Mild jaundice occurred in only one of the seven patients Bone marrow was hyperplastic in all

All the patients were subjected to splenectomy One patient died after operation The others were markedly improved but hematologic improvement tended to be gradual and prolonged rather than immediate and complete Examination of the spleen did not reveal any other disease that might have accounted for the hematologic disturbance The histologic picture was not characteristic or specific and generally no more than mild follicular hyperplasia could be demonstrated Failure to demonstrate excessive phagocytosis in spleens of these patients makes it doubtful that phagocytosis is the mechanism responsible for production of primary splenic panhematopenia Nor in the authors experience was the epinephrine test helpful in diagnosis or interpretation of the mechanism of this syndrome The rise in leukocyte count following administration of epinephrine results from appearance of increased numbers of lymphocytes in peripheral blood with little change in number of polymorphonuclear neutrophils

Role of the spleen in splenic panhematopenia is therefore not clearly defined especially when patients with this syndrome continue to show no excessive phagocytosis The authors suggest an alternative explanation namely that the spleen has a regulatory effect on bone marrow The anemia not clearly hemolytic may be the result of failure of proper discharge of erythrocytes from the marrow Presence of neutropenia and thrombocytopenia could be explained likewise on the basis of suppression of discharge of these elements from the marrow

Lecithinase Activity in Splenic Dyscrasias Mechanism of red blood cell destruction in vivo is extremely complex and only incompletely understood Though phagocytosis and fragmentation may sufficiently explain normal destruction of blood corpuscles in certain anemias the lytic factors become

eight clinical remission in the remaining eight was maintained despite hematologic relapse

When the spleen is enlarged from any cause leukopenia thrombopenia and anemia may occur this is the syndrome of hypersplenism Primary splenic disorder in which no associated disease is demonstrated is called primary hypersplenism Secondary hypersplenism occurs in many conditions perhaps the commonest is congestive splenomegaly of portal hypertension Splenectomy was performed on 10 patients with hypersplenism secondary to splenic or portal vein block cirrhosis or Gaucher s disease and on 1 patient with primary hypersplenism Normal blood levels were maintained after surgery in the 10 with secondary hypersplenism The patient with primary hypersplenism showed improvement for about three months when leukopenia recurred

Indications and Results of Splenectomy are discussed by Warren H Cole Leroy Walter and Louis R Limarzi[8] (Univ of Illinois) Data presented were obtained from study of 87 patients who had had splenectomy in the past 12 years

Results of splenectomy are best in hemolytic jaundice and thrombocytopenic purpura but even in these diseases extreme care must be exercised in selecting the patient Close cooperation between surgeon and hematologist is essential since the indications for splenectomy can rarely be classified as positive unless results of a sternal puncture as interpreted by a skilled hematologist are known

It is frequently very difficult to differentiate congenital hemolytic jaundice in which splenectomy is almost universally successful from acquired hemolytic jaundice in which poor results are common [Differential diagnosis is not difficult with modern methods demonstration of increased osmotic fragility of the red cells in members of the family in congenital hemolytic jaundice and pecific tests such as Coombs cold agglutinin acid hemolysin etc for acquired types — Ed] Anemia in the former condition is microcytic and in the latter macrocytic In many patients with acquired anemia there is no increase in red cell fragility In 28 patients with hemolytic anemia in the authors serie results were good to excellent in 23 with the congenital type but were good in only 1 of 5 with acquired hemolytic anemia

(8) A S g 129 702 723 M y 1949

hemolysis After splenectomy the spherocytosis may persist because of continued formation of lysolecithin in other parts of the body but in absence of the spleen the principal site of destruction is eliminated The fundamental difference in action of lysolecithin in stagnant and circulating blood is the best explanation for its striking action in the hyperactive spleen

Medical Aspects of Splenectomy H N Robson[7] (Univ of Edinburgh) states that splenectomy is of value in hemolytic disease in hemorrhagic disease due to thrombopenia and in hemocytopenia or reduction in blood cells occurring in the presence of an enlarged spleen In none of these groups is it known whether the blood changes are caused by remote influence of the spleen on the bone marrow or by local destruction of blood cells within the spleen

Of the many forms of hemolytic disease splenectomy is most consistently successful in familial hemolytic anemia In other forms of familial hemolytic disease such as Cooley s and sickle cell anemia splenectomy is rarely successful In acquired idiopathic hemolytic anemia results are variable in the acute and subacute forms splenectomy should be considered when repeated blood transfusions have failed to produce remission and in the chronic form when there are recurrent crises incapacitating anemia or formation of gallstones Acquired symptomatic hemolytic anemia in patients with reticulosis lipoidosis sarcoidosis tuberculosis and leukemia may respond to splenectomy In 13 patients with hemolytic anemia results of splenectomy were good in 4 with familial hemolytic anemia in 5 of 7 with the chronic form of acquired idiopathic hemolytic anemia and in 2 with the acute form of this disease

Splenectomy is of value in hemorrhagic disease only when thrombopenia is present Splenectomy is usually contraindicated in thrombopenia secondary to bone marrow disease though success was reported in a case of gold toxicity It is principally indicated in idiopathic thrombopenia Of 19 patients with idiopathic thrombopenic purpura treated with splenectomy complete clinical remission was produced in 16 These patients were observed for periods of 6 months to 17 years after operation Bleeding time capillary fragility and platelet counts were maintained at fully normal levels in

(7) Edinburgh M J 56 381 395 September 1949

POLYCYTHEMIA

The cause of this disease continues to attract speculation and to defy demonstration To the well known association with myelogenous leukemia recorded by Merskey Lawrence now adds four cases of multiple myeloma and an excellent account of his experiences with radioactive phosphorus in the treatment of the disease —Ed

Oxygen Saturation of Sternal Marrow Blood in Polycythemia Vera Observation of polycythemia at high altitudes and in certain forms of pulmonary and congenital heart disease has led to acceptance of the view that anoxia is an erythropoietic stimulus In polycythemia vera however oxygen saturation of arterial blood is normal Observers have therefore sought in bone marrow itself the evidence of anoxia in this disease Changes in capillaries and arterioles in bone marrow of patients with polycythemia vera have been demonstrated and decreased blood flow with subsequent anoxia as the erythropoietic stimulus has been postulated Chemical evidence of such anoxia has not been obtained however It has likewise been maintained that marrow anoxia is the stimulus to red cell production in anemia as for example after hemorrhage However studies of the percentage saturation and oxygen tension of bone marrow blood in dogs made anemic by bleeding have revealed no significant difference from the values in control animals These considerations led Bernard M Schwartz and Daniel Stats[9] (Mount Sinai Hosp New York City) to a study of the oxygen content in bone marrow blood in various disorders in man

Studies were done on 50 patients divided into four groups namely controls and patients with polycythemia vera anemia and anoxic anoxia From each patient within a period of several minutes specimens of bone marrow blood and brachial arterial blood were obtained Oxygen determinations were performed by the method of Roughton and Scholander

Results showed that percentage saturation of bone marrow blood was greater and the arterial bone marrow blood oxygen difference was smaller in patients with polycythemia vera than in controls This finding does not support the theory that there is local bone marrow anoxia due to decreased

(9) J Cl I v t g t on 28 736 740 J ly 1949

Although results are good in fully 90 per cent of patients having splenectomy for thrombocytopenic purpura they are rarely good in secondary or symptomatic purpura Best means of differentiating these two conditions is by bone marrow studies A marked increase in megakaryocytes is indicative of thrombocytopenic purpura this feature is of great prognostic value In 23 of 26 patients having splenectomy for thrombocytopenic purpura results were good to excellent and in the other 3 fair to good

The authors encountered 13 patients with what they classified as Banti s disease and 5 in whom they considered obstruction (anomalous or thrombotic) of the splenic vein to be the primary cause of the splenomegaly and portal hypertension Of the 13 patients with Banti s disease 5 died after splenectomy and in only 2 were results good In contrast four of five patients with obstruction of the splenic vein had good results from splenectomy The fifth patient still has occasional hemorrhages from esophageal varices and a portacaval shunt is contemplated Because results are so different the authors prefer to separate the two groups mentioned rather than classify them all as portal hypertension The authors are convinced that splenectomy should be performed in Banti s disease only in its early stages

Good results were obtained in four of five patients with Felty s disease which may also be classified as secondary panhemocytopenia although there was little improvement in arthritis There were no patients with primary splenic neutropenia or panhemocytopenia

Among the 87 patients there were 7 operative deaths 5 of which occurred in Banti s disease The authors recommend that careful study be made in this disease and splenectomy not be performed if hepatic insufficiency or other significant complications are present

[Moreover as emphasized in the discussion of this paper splenomegaly in this group of conditions is the result of splenic vein hypertension usually in turn a reflection of portal hypertension itself a sequel of cirrhosis At operation the point of obstruction must be located if possible If in the liver the splenic vein offers the best hope of a successful anastomosis to the left renal vein If splenectomy alone is performed, little if any relief of portal hypertension will result, and the splenic vein will not be available at a subsequent operation For this reason no surgeon unfamiliar with vascular anastomotic surgery should undertake to enter the abdomen with the objective of splenectomy in these patients —Ed]

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(9) J Cl n I t g t on 8 34 740 J ly 1949

blood flow in polycythemia vera but is compatible with either increase in blood flow or decrease in oxygen utilization by the marrow in this disease No significant differences were found between the values in anemic patients and those in controls In patients with anoxic anoxia due to chronic pulmonary disease or to right to left shunts in the heart, some of whom were polycythemic the percentage saturation of bone marrow blood with oxygen was lower than in controls

[In similar observations by Berk and others it was concluded that penetration of the bone marrow cavity by the sampling needle may so disturb conditions of local blood flow as to result in samples of blood not truly representative of the unaltered vascular relationships —Ed]

Relationship between Polycythemia Vera and Myeloid Leukemia Critical Review The exact nature of polycythemia vera (erythremia) is unknown However most theories regarding the fundamental pathology either link erythremia with erythrocytosis using anoxemia as a common denominator or consider the disease closely allied to myeloid leukemia

Clarence Merskey[1] (Univ of Cape Town) reviewed most reported cases in which a relationship between erythremia and myeloid leukemia was thought to have existed Leukemia was considered the diagnosis only if leukemic infiltrations outside bone marrow were proved at autopsy However such a minimal requirement for the diagnosis of leukemia was not always applicable Particularly the group of diseases known variously as chronic nonleukemic myelosis myeloid megakaryocytic splenomegaly and agnogenic myeloid hyperplasia required special consideration Leukocytosis was found to occur in erythremia and occasionally considerable myeloid hyperactivity was found In many of these patients the type of therapy used could have been the cause of excessive leukoblastic activity when it occurred Only two cases of erythremia were found in which no material therapy was used and in which the diagnosis was acceptable however one was associated with myelofibrosis and in the other the diagnosis could not be considered conclusive because there was no autopsy In nine cases the diagnosis of erythremia was acceptable but the patients had received some form of therapy only four were followed to autopsy and not all could definitely be considered to have had myeloid leukemia also In most cases the presence of all features necessary to state definitely that the

(1) Cl Proc. 8 150 162 Sept mber 1949

two conditions are related was not proved conclusively this was also true in cases of acute leukemia supervening in erythremia It is concluded that whereas some degree of myeloid hyperactivity is usually present in many cases of erythremia and in certain ones it may produce a leukemoid blood picture true erythremia associated with true leukemia is rare

In these cases anemia was not always present but there usually were primitive red and white cells in peripheral blood generally without the high number of leukocytes characteristic of leukemia There was a large spleen At autopsy foci of extramedullary erythropoiesis and leukopoiesis sometimes were found throughout the spleen and liver and occasionally in the kidney and lymph nodes Similar findings were associated with myelofibrosis and myelosclerosis It was not possible to know how frequently osteosclerosis or fibrosis occurred in patients with nonleukemic myelosis because the results of x ray examination of the skeleton were rarely recorded and fibrotic changes in bone marrow could only be detected by complete postmortem examination of the skeleton Patients with massive myeloid splenomegaly and osteosclerosis showed the same variations in duration of disease and in type of blood picture as patients with myeloid splenomegaly without osteosclerosis In both groups there were acute and chronic cases immature cells were usually present in circulating blood and blood studies sometimes showed a great increase in circulating leukocytes a high proportion of which sometimes were immature

On the basis of these cases it seems likely that erythremia can result in myelofibrosis or myelosclerosis If it can be concluded that this syndrome is essentially leukemia then erythremia and myeloid leukemia are certainly related It has been suggested that leukoerythroblastosis and myelofibrosis or myelosclerosis might occur simultaneously in response to a single but unidentified stimulus since all the cell types involved namely the osteoblast fibroblast hemocytoblast and megakaryocyte are derived from the same primitive mesenchymal reticular cell of Maximow Therefore it is possible that excessive hyperplasia of the totipotential cell involves all the blood elements (erythremia) predominantly affects myeloid elements along normal lines (nonleukemic myelosis) or goes on to uncontrolled proliferation (myeloid leu

kemia) On this basis it is easy to see how such a powerful therapeutic agent as irradiation could upset an already disturbed hemopoietic apparatus and predispose a patient to development of leukemia or anemia

Multiple Myeloma Associated with Polycythemia Report of Four Cases Simultaneous development of myeloma and polycythemia vera in one patient is of interest for a number of reasons Both conditions chiefly involve bone marrow Their etiology is unknown and their simultaneous appearance is rare Review of the literature reveals three reports of polycythemia vera associated with possible myeloma John H Lawrence and Robert L Rosenthal[2] (Univ of California) report four cases of definite myeloma associated with polycythemia The patients were first studied and followed because of polycythemia Myeloma was an unexpected development or finding

CASE 1—Man 59 had symptoms and a blood picture consistent with diagnosis of polycythemia vera No symptomatic improvement followed treatment with radioactive phosphorus although red cell count fell to normal after administration of 35 33 mc in seven months Two years after discovery of polycythemia the patient presented symptoms due to a destructive lesion of the ninth dorsal vertebra He died one year later and at autopsy the lesion was found to be a myeloma composed predominantly of plasma cells

CASE 2—Woman 50 was found to have polycythemia while living at a high altitude It disappeared when she was at sea level She complained of pains in the arms and legs and was found to have Bence Jones proteinuria Diagnosis of myeloma was established by discovery of 9 6 per cent plasma cells in aspirated sternal marrow At the time of this report she had been relatively asymptomatic for almost one year

CASE 3—Woman 65 had symptoms suggestive of polycythemia vera of eight months duration Although the red cell count was not significantly elevated an elevated hematocrit reading history and florid appearance were strongly indicative of this disease Bone marrow study revealed 13 per cent plasma cells and x ray examination showed two areas of bone rarefaction

CASE 4—Man 56 had known polycythemia vera for two years He had a brief terminal illness marked by renal failure Autopsy revealed multiple myeloma.

The authors speculate on the part played by myeloma in causing or contributing to polycythemia in each of these cases It is possible that proliferating cells of both the red cell and the myeloma series originate from the same stem

(2) Am J M Sc 218 149 154 Aug t 1949

cell with certain *unknown* factors determining the type of cell produced In these cases the stem cell *may* first have differentiated into the red cell series to cause the elevated red cell count which *later* decreased when the stem cell differentiated into myeloma cells

Since these *patients* were studied initially for polycythemia unexpected discovery of myeloma *provides* some information about the course of the latter disease In Case 2 there have been no symptoms which could *be definitely* attributed to myeloma for one year since its discovery It is evident that myeloma can be present in a *latent* state Little is known about this latent *state* and its duration

Whether radioactive phosphorus given in Case 1 could have been a factor in causing myeloma cannot be answered but it is unlikely that such small doses could induce neoplasm so soon after radiation therapy

Control of *Polycythemia* by Marrow Inhibition Ten Year Study of 172 Patients with polycythemia *from* various causes is reported by *John H* Lawrence[3] (Univ of California) There was no clearcut differentiation *between* primary and secondary polycythemia although most patients with the primary disease *presented* the classic picture and most of those with the secondary form had an obvious cause for the elevated red cell count However there were patients in between these classifications in whom the question of *anoxia arose* This led to a consideration of whether an anoxic stimulus may not be a factor in all cases of polycythemia

Radioactive phosphorus (P^{32}) was given 121 patients with polycythemia vera aged 19 75 at time of onset (average 50 7) and follow up studies were made to *evaluate* this form of therapy with *reference* to life expectancy or prolongation of life Palpably enlarged spleens were *present* in 65 per cent After therapy the spleens became smaller White blood cell counts above 10 000 were *noted* in 68 *per* cent initially and of these 38 *per cent* had myelocytes or immature white cells This finding is of interest because of the *relation* between polycythemia *vera* and leukemia and the frequent occurrence of leukemia as a complication of polycythemia vera Of those having immature white cells 69 per cent had received previous therapy After P^{3} therapy immature white cells were

(3) J A M A 141 1338 Sept 3 1949

found in only 27 per cent of those originally having such cells About 4 per cent of the total series had myelocytes in the peripheral blood after P^3 therapy but not before No patient with a normal total white cell count initially had myelocytes in the peripheral blood A third of the patients had elevated blood pressures and a third of these showed a fall in pressure after P^3 therapy There was peptic ulcer or a history of it in 11 5 per cent and a history of thrombosis in 14 8 per cent

When necessary arterial blood oxygen saturation studies were done to rule out secondary polycythemia as were special pulmonary and cardiac studies Criterion for diagnosis was a red blood cell count of 7 000 000 or over unless there was clearcut evidence of the diagnosis in the past or an enlarged spleen with a definitely elevated red cell count In borderline cases the red cell mass as determined by P^3 labeled cells and measurement of red cell production with Fe^{59} were often helpful in diagnosis

During 1939–42 30 patients were treated Since that time this group has received one course (usually two injections of 3 6 mc) on the average of every three years Of the 121 patients 47 8 per cent received only one course of therapy Of the first 30 patients 17 per cent remained normal (at the time of this report) for over three years after the single course of therapy Of the group treated during the first five years of the study 28 per cent had only one course of therapy some of them did not need retreatment after four to eight years

There have been 21 deaths causes being generalized arteriosclerosis (5) leukemia (5) neoplastic disease (3) coronary occlusion (3) cardiac failure (2) portal thrombosis (1) anemia and leukopenia (1) and cerebral thrombosis (1) Average age at death was 67

Since four of the five patients who died of leukemia showed some suggestion of it when first seen there appears to be no significant increase in the incidence of this complication after P^3 therapy Similarly there was no evidence of the consistent occurrence of other complications which might be related to the treatment For example there was no evidence that neoplasms were induced by this therapy Of special interest was the low incidence of thromboses after P^3 therapy Lawrence concludes that patients with polycythemia vera who are properly treated have as favorable an outlook as do

patients with diabetes mellitus treated with insulin or those with pernicious anemia treated with liver

[This excellent article illustrates the satisfactory remissions that can be obtained in this disease as here with P^3 or by others with spray irradiation —Ed]

LEUKOCYTOSIS AND LEUKOPENIA

Production in Vitro of L E Cell Phenomenon Use of Normal Bone Marrow Elements and Blood Plasma from Patients with Acute Disseminated Lupus Erythematosus is described by Malcolm M Hargraves[4] (Mayo Clinic) A characteristic L E cell (Fig 78) observed in bone marrow of patients with acute disseminated lupus erythematosus was in no case found by direct smear of bone marrow L E cells observed were always in the material outside the touch preparation where the material had come in contact with heparinized plasma Heparin was considered the agent possibly responsible and preparations were made using other anticoagulants including oxylate and citrate The L E cell appeared in all these preparations Consequently venous blood was added to any anticoagulant centrifuged and smears were made from the buffy coat layer in cases in which bone marrow had been positive L E cells were found

A small centrifuge bottle with a narrow intermediate section and expanded portions above and below for use with the venous blood permitted concentration of the buffy coat in a narrow column By this procedure the L E cell has been demonstrated in an occasional case when bone marrow preparations have failed because of the small amount of material obtained The phenomena most commonly observed in material from peripheral blood have been nucleolysis and agglutination in which neutrophilic leukocytes cluster around the rather homogeneous mass of nuclear material and attempt to engulf it

These observations suggested that the material responsible for the nucleolysis agglutination and phagocytosis might be in the plasma of patients with acute disseminated lupus and that it might be possible to produce L E cells by use of bone marrow from patients who did not have the disease Plasma

(4) P oc St ff Meet M y Cl 4 234 237 Ap 27 1949

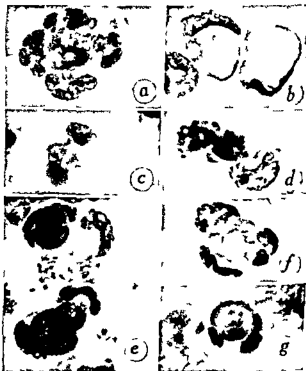


Fig 78—*a* f r n t ph l polym phonucl le kocytes (n t oph l) lus te ed b ut ma of n l m te l dem st t g chem t t ff ct of th f e lysed nucl m te l *b* two L E ell as een in n v tro p ep rat f blood pl ma fr m p t t w th cute d em t d lup s yth mat s s a d bo m w eleme t f om p t nt w th n rm l b n m row Some ch om t n p tt rn s ble gulfed m t al two-l b d ne t oph l d m t at g n le l s of e of its lob *d* th e d tly m t t figu n wh h th ck sp reme h omas m hav u dergone ly s a d nt m s i bo t t be e gulf d by ph gocyt c neut phil N t ne tr ph l p eud pod t d g long s d f t ll la cl m *e* tw n t ph l t of ng lfi g n le m s Note e f co tr t ind cat g that ll h d su d d n ph gocyt g l g p t n tha has the oth The e 1 L E ll n me fi ld w th wh t appe t be two s pa at n l masses w th d g t v cu l f L E ell *f* a ther l mp f three neu troph l tt ct d t f ee nucl ma In s p tal p parat o wh ct ph gocyt can be se n s m l clump ha e b en b rv d a d wh o leuko cyt ha s eded n engulfi g h m t t c m t al oth r l kocyt mo ff to th fi ld *g* l c L E ll d lt of n cleoly o h m toly g gl t nat on or ch notax and phagocyt w th two l bed t oph l onta g d d g t v cu l filled w th ly d n le m t l N t oth m se f f ee nu l a m t l fi ld All m g fi t n × 930 (C u t y f ll g es M M Pr Staff M t M yo Cl n 24 34 237 Ap 27 1949)

obtained from venous blood of patients with acute dis em inated *lupus erythematosus* was then incubated with plasma bone marrow material obtained from patients with various other diseases Typical L E cells as well as the phenomena of nucleolysis and agglutination were observed

These observations on the L. E. cell add weight to the hypothesis that acute disseminated lupus erythematosus is a result of hypersensitivity. The L. E. cell phenomenon is evidently immunologic in nature. Use of peripheral blood in a procedure for diagnosis of lupus is possible but as yet would be premature. Too few cases have been studied to establish its utility in this regard, although it can be anticipated that a positive finding in examination of peripheral smears would have significance comparable to that of a similar finding in examination of bone marrow.

[Leukocytes from the buffy coat of centrifuged samples of peripheral blood may also be incubated in the plasma to be tested.—Ed.]

Lymphocytic Leukemoid Reaction of Blood Associated with Miliary Tuberculosis. Frank H. Gardner and Stacy R. Mettier[5] (Univ. of California) report two cases in which there was a lymphocytic leukemoid response to miliary tuberculosis. Clinical diagnosis in both cases was lymphocytic leukemia, but autopsies revealed diffuse miliary tuberculosis involving all hemopoietic tissues and no evidence of leukemic infiltration. Both patients had granulocytopenia and anemia. In one, chronic tuberculosis was of 43 years and in the other of 28 years duration. The findings emphasize that it may be impossible to distinguish between a terminal leukemoid blood picture and true leukemia. There have been other reports of blood pictures similar to those of myelocytic and lymphocytic leukemia occurring in patients with miliary tuberculosis.

Rossle observed patients with lymphocytic leukemia without adenopathy or hepatosplenomegaly, but microscopic examination of bone marrow revealed leukemic infiltration. In one of the authors' cases autopsy findings of young and old tubercles throughout the organs and lymph nodes suggested repeated bacteremia. Several sections of sternal and vertebral marrow revealed extensive single and conglomerate tubercle formation with striking caseation and trabecular bone destruction. Aside from tubercle formation there were normal quantitative and qualitative relations of myelopoietic and erythropoietic series. Megakaryocytes were adequate in number (Fig. 79). The persistent lymphocytosis might result from persistent irritation of the lymphoid tissue and marrow by progressive miliary tuberculosis. Feldman and Stasney ex-

(5) Blood 4:767-775, J... 1949.

plained the myelocytic leukemoid blood response in tuberculous rabbits receiving tuberculin injections as an allergic response of bone marrow There is no experimental work to



F g 79—Bon ma w Ep th l al p oc d d by m w f n rmal arch t tur × 1 0 (C tesy of Ga d F H a d Mett S R Blood 4 767 775 J 1949)

indicate that lymphocytosis or a lymphatic leukemoid reaction is an allergic response to miliary tuberculosis

Rapid Slide Test for Heterophil Antibody in Infectious Mononucleosis William C Moloney and Lucy Malzone[6] (Tufts College) describe a practical screening test for detecting clinically significant amounts of heterophil antibodies in cases of infectious mononucleosis

METHOD—On a glass slide at room temperature 0 1 cc. defibrinated sheep blood was mixed with 0 2 cc serum to be tested Results were positive only if 3 or 4 plus macroscopic clumping occurred within 30 60 seconds The heterophil antibody test was carried out on the same serums using the Paul Bunnell method and a serum dilution of 1 128 was considered the lowest positive level Sheep cells were preferably used fresh but defibrinated sheep blood kept at 5 C for two weeks gave reliable results Inactivation of serum was unnecessary Serums stored in the icebox lost potency slowly but if kept in the deep freeze the heterophil antibody was well preserved for long periods The heterophil antibody in infectious mononucleosis is active at 37 C as well as at lower temperatures

Of 41 patients with infectious mononucleosis the slide test

(6) Blood 4 72 727 J 1949

was positive for 35 and the Paul Bunnell test for 34 Of 53 patients with cirrhosis of the liver and 21 with acute infectious hepatitis the slide test was positive at room temperature for 7 with cirrhosis but negative for all at 37 C The Paul Bunnell reaction was negative for all Only 1 patient with multiple myeloma among 58 with a variety of neoplastic diseases had positive results in the slide test and none had positive Paul Bunnell reactions The serums of 95 pregnant women and 23 cord blood specimens showed no heterophil antibodies Results of Paul Bunnell and slide tests at 37 C were negative in seven patients with acquired hemolytic anemia Of 15 isoimmunized women only 1 had positive reactions to Paul Bunnell and slide tests The mother was O Rh positive and the father Rh positive A_1 A Their second child was A O Rh positive An anti A agglutinin developed in the mother The antibody in this case was apparently related to the Forssman type rather than that found in infectious mononucleosis

The rapid slide test can give positive results with cold agglutinins (which may be abolished by warming to 37 C) or Forssman antibodies (which may be absorbed by guinea pig kidney) There was no evidence that blocking incomplete or hyperimmune heterophil antibodies occur in infectious mononucleosis

Rapid Macroscopic Test for Infectious Mononucleosis Method for Preservation of Sheep Cells The ordinary method of blood examination for heterophil antibodies is time consuming and requires fresh sheep blood F Rappaport (Tel Aviv) and M Skariton[7] (Petah Tikvah Israel) describe a rapid *qualitative and quantitative method for determination* of heterophil antibodies and a technic for preservation of sheep s blood cells

METHOD —The preliminary qualitative method is a slide agglutination test In most ca es active serum is used To 1 drop of the unknown serum (fresh or inactivated) is added 1 loopful of concentrated sheep s blood corpuscles washed three or four times with saline solution the two are mixed thoroughly with a glass rod If no agglutination appears the serum is considered negative Typical agglutination constitutes a positive reaction and then requires quantitative evaluation

For quantitative evaluation a series of dilutions is made ranging from 1 7 to 1 3 584 Physiologic salt solution 0 4 ml is placed

(7) Am J Cl P th 19 665 667 J ly 1949

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(6) Blood 4 7 7 7 J 1949

Gm per cent Patients with aplastic anemia required frequent transfusion whereas those with chronic agranulocytosis did not

Four patients were women and four patients were aged 22 27 when they came under treatment The woman aged 46 at the time leukopenia was recognized may well have had the disease many years Before agranulocytosis was diagnosed all had been exposed to factors which might possibly have damaged bone marrow such as hair dye sulfonamides lead benzyl benzoate and mumps

The disease was characterized by attacks of severe infection from relatively trivial causes They included inflammation of the lips gums mouth and throat severe reactions to dental extraction otitis media digital and cutaneous sepsis suppurative lymphadenitis urinary infection septicemia and unexplained fever Intervals between attacks ranged from a few days to six years Between attacks the patients were fairly well though they lacked vitality Average duration of illness in the four survivors is now more than five years and there is no evidence of progressive deterioration

Marrow smears were cellular in two patients and acellular in three The main qualitative change was an increase in proportion of myelocytes and a great decrease in proportion of segmented neutrophils The only remedy of proved efficacy was penicillin for control of acute attacks When bone marrow is cellular in patients of this type splenopathic neutropenia may be suspected but is unlikely in the absence of splenomegaly and increased blood destruction The authors suggest that these cases are variants of chronic aplastic anemia in which the main impact of the disease is on white cells

Cyclic Agranulocytosis Paul A Owren[9] (Univ Hosp Oslo) reports a case

Man 23 in spring 1939 had the first of many attacks of fever and sore throat which lasted a week and recurred in about 14 day Enlarged tonsil were found and since relapsing angina was suspected as the cause tonsillectomy was done However relapses continued with surprising regularity for five years until death in 1944

Two days before each relapse the patient experienced fatigue anorexia and irritability *Simultaneously or a little later sore spots* appeared in the buccal mucosa Some became covered with grayish white masses surrounded by a red halo and others progressed to

(9) Act med Scand 134 8 97 1949

in the first tube and 0 25 ml in each of the remaining nine tubes To the first tube 0 1 ml patient s serum is added and mixed From this tube 0 25 ml is transferred to the second tube and mixed From the second tube 0 25 ml is transferred to the third etc To each tube 0 1 ml suspension of washed sheep cells is added Tubes are centrifuged immediately for two minutes at 3 000 rpm Results are read after gentle shaking The last tube containing single clumps indicates the limit of reaction

In the authors experiments every serum was tested by three methods the qualitative slide method the original Paul Bunnell method (with inactivated serum) and the quantitative rapid method Results obtained by these methods were identical The qualitative test first gives a positive result when the quantitative test shows agglutination in a dilution of 1 56 This limit should be regarded as suggesting infectious mononucleosis whereas a dilution of 1 112 constitutes a positive reaction

Since sheep s blood keeps in the refrigerator for only about five days it may be difficult in routine laboratory work to keep on hand a supply of sheep s blood that is satisfactory for use By addition of an equal part of 5 per cent Borax solution of pH 7 4 7 6 to defibrinated sheep s blood the latter can be preserved in the ice box for at least two months without undergoing hemolysis Addition of Borax does not interfere with the reaction

The authors method has the advantage that inactivation is omitted and results may be obtained quickly since it is not necessary to incubate for 2 hours or store on ice for 24 hours

Chronic Agranulocytosis E B Adams and L J Witts[8] (Radcliffe Infirm Oxford) studied five patients in whom *neutropenia (neutrophil count below 1 500/cu mm)* was apparently a primary condition The only constant features were leukopenia (total white cell count below 4 000/cu mm) and attacks of agranulocytic infection There was no evidence of increased blood breakdown no deficiency of iron or liver and no leukemic or other infiltration Mild anemia was present in some of the five *and the distinction between chronic* agranulocytosis and aplastic anemia is an arbitrary one It was the authors practice to diagnose aplastic anemia in patients of this type if the hemoglobin without treatment was below 10 Gm per cent and chronic agranulocytosis if it was above 10

(8) Q rt. J Med 18 1 3 185 July 1949

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(9) A ta med. Sca d 134 87 97 1949

mucosal necrosis leading to deep ulcerations accompanied by regional swelling of lymph nodes and rise in temperature Ulcerations were localized to the inner side of lips and cheeks tonsillar region and posterior pharyngeal wall Temperature rose evenly to 102.2 104 F and returned by lysis to normal in a few days Regularly during febrile periods heavy gingivitis developed with edematous and bleeding interdental papillae purulent secretion and intense halitosis Some relapses were associated with necrotic ulcerations of skin in the anal region face and extremities The primary eruptions were vesicles which ruptured and gave rise to ulcerations Several attacks were associated with conjunctivitis When attacks were over ulcerations healed rapidly

The highest granulocyte counts were found in the first half of the symptom free interval During the following days the granulocyte count rapidly decreased until there was complete agranulocytosis or severe granulocytopenia one to three days before the next temperature rise The agranulocytic phase lasted three to five days and then while the temperature fell granulocytes again increased. The postfebrile increase of granulocytes was associated with a shift to the left with numerous staff cells metamyelocytes and some myelocytes in the peripheral blood At the same time pronounced toxic granulation appeared Eosinophils and basophils showed no definite cyclic changes but monocytes showed slight cyclic changes in the opposite direction to the granulocytes Lymphocyte count remained normal Plasma cells appeared in small numbers toward the end of the agranulocytic phase Hemoglobin level and red cell counts remained normal Marrow granulocytopoiesis showed cyclic variations in constant relation to peripheral blood findings Clinical examination of the patient otherwise revealed normal findings

All remedies suggested in the literature for cyclic agranulocytosis were used but none was effective These included pentnucleotide roentgen treatment liver therapy long term vaccination with hemolytic streptococci vitamins blood transfusions antiallergic treatment with epinephrine ephedrine salicylic acid and detoxin and finally splenectomy The only effective measure used was antibiotic treatment of the mouth infection a result rather than a cause of agranulocytosis

Because of the theory that cyclic agranulocytosis results from an allergic reaction with neutralization of antibody followed by reaction free antianaphylactic period cutaneous tests were made with a series of antigens Results however were equivocal Minimal doses of hemolytic streptococci produced extremely strong reactions with large infiltrations and formation of secondary abscesses but repeated injection did not show any clearcut effect on granulocyte counts or cyclic variations in bone marrow

The theory has been proposed that granulocytopenia results from excessive leukolysis in the spleen and a case of relapsing agranulocytosis has been reported in which symptoms disappeared after splenectomy Negative result of

splenectomy in the present case however suggests that the spleen is not important in the pathogenesis of cyclic agranulocytosis

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LEUKEMIAS AND RELATED DISORDERS

The first two articles demonstrate that diagnosis from bone marrow biopsy is possible only when typical cellularity can be demonstrated For this reason conditions with late or nonhomogeneous involvement of the bone marrow are unlikely to be susceptible of early diagnosis by bone marrow puncture It is a good general rule that without definite disturbance of the peripheral blood picture (indicating diffuse marrow involvement) marrow biopsy will not be diagnostic In the lymphoma group the difficulty of diagnosis even from sections of lymph nodes means that needle biopsy of the marrow will be as futile as is usually needle biopsy of a definitely involved lymph node In our hands needle biopsy of the bone marrow is used largely as a procedure confirmatory of a diagnosis usually inferred from peripheral blood examination If a cellular marrow is not clearly in evidence it then becomes necessary to carry out trephine biopsy to determine the nature of the hyperplasia whether fatty fibrotic or otherwise —Ed

Evaluation of Sternal Aspiration as Aid in Diagnosis of Malignant Lymphomas In Hodgkin s disease thoracic and abdominal nodes are involved much more commonly than are the superficial cervical nodes Because of the inaccessibility of thoracic and abdominal nodes for biopsy Talbert Cooper and Charles H Watkins (Mayo Clinic) attempted to evaluate clinical usefulness of sternal bone marrow aspiration for obtaining material of diagnostic significance in malignant lymphoma

Simple needle aspiration of sternal bone marrow was performed on 15 unselected patients with Hodgkin s disease 10 with lymphosarcoma and 2 with follicular lymphoma Diagnosis was based on results of lymph node biopsy autopsy or both With the Illinois sternal aspiration needle about 2 cc sternal marrow substance was aspirated and transferred immediately to a paraffin lined container and mixed gently with a minute pinch of heparin powder as an anticoagulant Grossly visible particles of marrow substance were smeared gently on the surface of a glass slide

Criteria used for diagnosis of Hodgkin s disease of bone marrow were similar to those used for its diagnosis in other tissues and organs Hyperplasia of reticular cells is often the

(2) Blood 4 534 549 My 1949

dominant change However because Hodgkin s is characterized by pleomorphism diagnosis rests finally on demonstration of Reed Sternberg cells There is no certain way of distinguishing these cells from megakaryocytes However nuclei of Reed Sternberg cells are round oval lobulated multilobed or multinucleated whereas megakaryocytic nuclei though often multilobed are always single with generous more uniformly distributed chromatin and a fine chromatin parachromatin pattern The outstanding characteristic of the Reed Sternberg cell is the prominent nucleolus which is usually lacking in the megakaryocyte or megakaryoblast Cytoplasm of the normal megakaryocyte contains characteristic azurophilic granulation when stained with polychrome dyes In addition pseudopodia with apparent platelet formation are often observed The generous cytoplasm of the Reed Sternberg cell has a faintly basophilic granular appearance with Wright s stain and the cell membrane is often indistinct Satisfactory section preparations were obtained in nine instances but in none were lesions suggestive of Hodgkin s disease demonstrable Lesions of bone marrow in Hodgkin s disease may be focal and of microscopic proportions or extensive and grossly demonstrable When small focal lesions exist chance alone might account for disappointing results on attempted needle aspiration

In lymphosarcoma all elements of the normal lymph node may be represented and there is no diagnostic cell Cells range from typical small lymphocytes through larger atypical cells with indented hyperchromatic nuclei and relatively little cytoplasm to lymphoblastic cells with reticular nuclear structure sometimes containing nucleoli and a basophilic often vacuolated cytoplasm Lymphocytic lymphoblastic and reticulum cell varieties of lymphosarcoma have been commonly described In 7 of the 10 cases of proved lymphosarcoma abnormal lymphocytic cell types were encountered on sternal aspiration and in 3 cases bone marrow infiltrations diagnostic of lymphosarcoma were demonstrated in fixed section preparations

In two cases of follicular lymphoma specimens of sternal marrow presented no striking abnormalities However because of the apparently close relation of this disease to lymphosarcoma it is felt that study of a larger number of cases

may prove the procedure to be of some diagnostic value The authors conclude that as an aid to diagnosis in obscure malig nant lymphoma sternal aspiration is likely to prove of great est value in lymphosarcoma [in which surgical biopsy of a lymph node is usually possible and certainly far more satis factory —Ed]

Sternal Marrow Studies in Hodgkin s Disease Review of Literature and Report of 35 Cases On the basis of their study Louis R Limarzi and Jerome T Paul[3] (Univ of Illi nois) conclude that the most constant finding in bone marrow in Hodgkin s disease is myeloid and megakaryocytic hyper plasia The morphologic pattern of the granulopoietic tissue is that seen in chronic toxic states The panhyperplasia of bone marrow simulates that of Banti s disease (splenic ane mia) A pathologic type of megakaryocytopoiesis involving the lymphoid megakaryocytes is observed in some cases of Hodgkin s disease These produce atypical forms of platelets Reed Sternberg cells are not seen in aspirated sternal marrow or in histologic sections of bone marrow particles from such material Detailed cytologic studies on bone marrow mega karyocytes in cases of Hodgkin s disease indicates that the giant cells in Hodgkin s granuloma are not similar or related to the platelet forming cell The finding of increased num bers of normal or atypical plasma cells eosinophils and reticular cells is neither a constant nor a specific pattern of the bone marrow in Hodgkin s disease Eosinophilia of bone marrow cannot be correlated with peripheral blood eosino philia

Evidence at hand definitely indicates that the cellular mar row elements removed by sternal aspiration in most cases of Hodgkin s disease are not obtained from the pleomorphic lesion characteristic of Hodgkin s granuloma There are sev eral reasons for this failure to observe the specific tissue in sternal aspirated material not every sternum is involved in Hodgkin s disease the scattered specific focal lesions usually occupy such a small proportion of the marrow cavity that on the basis of chance they may not be aspirated by the sternal needle the specific lesions in bone marrow tend to have much fibrous tissue making aspiration more difficult The authors emphasize that unless specific tissue is ob erved

(3) Am J Cl n P th 19 929 961 O t be 1949

dominant change However because Hodgkin s is characterized by pleomorphism diagnosis rests finally on demonstration of Reed Sternberg cells There is no certain way of distinguishing these cells from megakaryocytes However nuclei of Reed Sternberg cells are round oval lobulated multilobed or multinucleated whereas megakaryocytic nuclei though often multilobed are always single with generous more uniformly distributed chromatin and a fine chromatin parachromatin pattern The outstanding characteristic of the Reed Sternberg cell is the prominent nucleolus which is usually lacking in the megakaryocyte or megakaryoblast Cytoplasm of the normal megakaryocyte contains characteristic azurophilic granulation when stained with polychrome dyes In addition pseudopodia with apparent platelet formation are often observed The generous cytoplasm of the Reed Sternberg cell has a faintly basophilic granular appearance with Wright s stain and the cell membrane is often indistinct Satisfactory section preparations were obtained in nine instances but in none were lesions suggestive of Hodgkin s disease demonstrable Lesions of bone marrow in Hodgkin s disease may be focal and of microscopic proportions or extensive and grossly demonstrable When small focal lesions exist chance alone might account for disappointing results on attempted needle aspiration

In lymphosarcoma all elements of the normal lymph node may be represented and there is no diagnostic cell Cells range from typical small lymphocytes through larger atypical cells with indented hyperchromatic nuclei and relatively little cytoplasm to lymphoblastic cells with reticular nuclear structure sometimes containing nucleoli and a basophilic often vacuolated cytoplasm Lymphocytic lymphoblastic and reticulum cell varieties of lymphosarcoma have been commonly described In 7 of the 10 cases of proved lymphosarcoma abnormal lymphocytic cell types were encountered on sternal aspiration and in 3 cases bone marrow infiltrations diagnostic of lymphosarcoma were demonstrated in fixed section preparations

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Amyloidosis in Hodgkin's Disease is discussed by Stanley L Wallace Daniel J Feldman Irving Berlin Charles Harris and Irving A Glass[4] (New York City) Although associa tion of amyloidosis and Hodgkin s disease has been known for a long time review of the literature reveals only 29 cases of Hodgkin s disease in which concurrence of amyloidosis was demonstrated histologically or suggested by clinical studies

From analysis of these cases and of one observed by the authors coexistence of Hodgkin s disease and amyloidosis appears to be more than a coincidence All reported cases are typical of the secondary type of amyloidosis i e involvement chiefly of the liver spleen kidneys and adrenals In primary amyloidosis the heart lungs skin mucous membranes and tongue are usually involved Although a small percentage of primary cases may show a secondary type of distribution the fact that all available reported cases fall into the latter category tends to rule out a casual association of Hodgkin s disease and primary amyloidosis There seems to be no asso ciation between amyloidosis and any specific form of Hodg kin s disease since reported cases fall into all categories and have the same sex and age distribution as Hodgkin s disease in general

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(4) A J M d 8 55 557 Ap l 1950

nels by Hodgkin s tissue as well as by hypoproteinemia sec ondary to the albuminuria of renal amyloidosis However uncomplicated Hodgkin s disease even with renal involve ment has not been reported as producing albuminuria In 11 of 15 adequately studied cases of associated amyloidosis and Hodgkin s disease pronounced albuminuria was noted In three of the other four cases at least a trace of albumin was found in the urine It can therefore be presumed that pro teinuria occurring during Hodgkin s disease points to a com plicating factor and amyloidosis must be carefully searched for as a possible cause of the urinary findings Congo red tests were made in five reported cases and in the authors case All could be interpreted as positive if 60 100 per cent absorption of congo red from the blood is considered diagnos tic of amyloid disease It is therefore concluded that presence of proteinuria and significant absorption of congo red from the blood are the most reliable criteria for determining pres ence of amyloid in Hodgkin s disease

Chronic Nonleukemic Myelosis Report of Six Cases is made by Clarence Merskey[5] (Univ of Capetown South Af rica) The name chronic nonleukemic myelosis seems appro priate for certain conditions described under a wide variety of other names (chronic splenomegaly with anemia and my eloid reaction of blood splenomegaly of myeloid type without myelocythemia myeloid megakaryocytic splenomegaly spleno megaly with myeloid transformation hepatolienal hemopoi etic endotheliosis and agnogenic myeloid metaplasia) All these refer to a condition in which there may or may not be anemia but in which there are usually primitive red and white cells in peripheral blood though the great increase in leuko cytes characteristic of leukemia is usually absent The spleen is enlarged and at autopsy foci of extramedullary hemopoiesis may be found in spleen and liver and to a lesser extent in other organs such as kidneys and lymph nodes The essential fea ture is hyperplasia of leukopoietic tissues which results in an increase in white count and in a degree of immaturity in white cells of peripheral blood Bone marrow especially shows gross overgrowth of cells of the myeloid series though even in marrow the hyperplasia appears relatively orderly in na ture Consequently marrow does not display the invasive char

(5) A h I t M d 84 277 292 A gu t 1949

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(4) Am J Med 8 55 557 Ap I 1950

the worse the prognosis and the greater the disability The more the condition resembles nonleukemic myelosis the more chronic the disease and the better the prognosis The disease was chronic in these six patients In five anemia was either absent or mild in none were myeloblasts found in peripheral blood even myelocytes were scanty in four patients total white cell count showed all grades of increase but in general was less than that characteristic of chronic myeloid leukemia Immature red cells were found only in small numbers in peripheral blood

This syndrome is also related to polycythemia vera and forms a connecting link between polycythemia vera and true leukemia Merskey suggests that the syndromes of polycythemia vera nonleukemic myelosis and true leukemia and even possibly osteosclerosis and myelofibrosis have a common genesis

↓ The following four articles are concerned with multiple myeloma a neoplastic disease usually con idered to be due to plasma cell proliferation The increasing use of plasma protein determinations and especially of needle puncture of the bone marrow is leading to more frequent diagnosis of the condition —Ed

Multiple Myeloma Willis M Fowler and Jack D Gordon[6] (State Univ of Iowa) analyzed clinical and laboratory findings in 52 patients with multiple myeloma This disease was first recognized by presence of a substance in the urine now known as Bence Jones protein For a long time Bence Jones proteinuria was considered one of the important diagnostic criteria but it is now known that it occurs in only about half the patients with multiple myeloma and also in patients with other types of bone lesions In addition Bence Jones proteinuria may appear only intermittently rather than constantly In the present series it was encountered in 34 6 per cent of patients in whom urine tests were done Its presence or absence in an individual case has limited diagnostic value and no prognostic significance nor can its presence be correlated with the presence of ordinary albuminuria or with plasma protein level When found in urine however Bence Jones protein suggests multiple myeloma and should lead to further diagnostic procedures

Multiple myeloma occurs in the later decades and is more common in men than in women Pain usually in the back

(6) Am P t. 1 449 460 M y 1950

acteristics seen in true leukemia The course is prolonged anemia tends to be slight and disability is often negligible for some years Bone marrow is not leukemic in that it does not show immaturity at the myeloblast level which is characteristic of true leukemia nor are myelocytes necessarily numerous Nevertheless the condition may be only a mild variant of leukemia differing only in degree rather than in any fundamental characteristic

In the six cases studied by Merskey the clinical picture was not particularly characteristic All patients were elderly and in all the disease followed a somewhat symptomless course Chief symptoms were general such as vague feelings of ill health and lack of strength and were usually related to degree of anemia In two cases the red cell count was normal One patient had mild and another severe anemia whereas in two patients the count almost reached polycythemic levels Thrombocyte number was within normal range in four patients but in two it was 1 500 000 and more/cu mm White cells were increased in all patients and showed varying degrees of immaturity two patients showed immature red cells as well None had myeloblasts in peripheral blood but in all the cells of the polymorphonuclear leukocyte series were grossly increased both relatively and numerically There were no constant correlations between increases in red cell series in white cell series and in thrombocytes Autopsy material demonstrating hyperplasia of bone marrow was available in two cases and in three others hyperplasia in situ was shown in sections of bone marrow taken during life

This rather mixed collection of cases included one case of true chronic myeloid leukemia one of osteosclerosis with myeloid reaction one of possible chronic hemolytic anemia and three of (possibly) nonleukemic myelosis It was not possible to make a diagnosis during life in the case of osteosclerosis despite x ray examination of bones and biopsy of aspirated marrow sections Chronic hemolytic anemia can usually be diagnosed but in this patient the only evidence of that disease was a consistently elevated reticulocyte count the patient refused marrow aspiration The real difficulty in diagnosis lay in differentiation of these disorders from true chronic myeloid leukemia Differences were really only in degree It appears that the greater the incidence of leukemic features

localized to a single or a few foci the process is usually generalized and typical myeloma or plasma cells are evident in the sternum ribs ilium or vertebra in the early stages This procedure has also emphasized how frequently the lesion is of the plasma cell type The number of plasma cells seen on a marrow smear is variable but in the authors experience is greater than 10 per cent of nucleated cells The mature plasma cell is usually oval with a deep blue cytoplasm having an irregular or blotchy staining reaction It appears to contain bluish granules although granules as such are

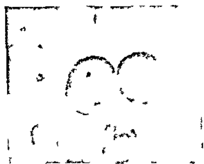


Fig 80—G p f f pl m ll w th tw mm t f m (Courte y f F wl W M d G don J D Am P t 1 449 460 M y 1950)

seldom found There may be a perinuclear clear or light staining area or the light staining area may be ovoid and located at the side of the nucleu rather than encircling it In the immature cell the outline is often irregular Vacuolation of the cytoplasm is frequent and the nucleus is usually eccentrically placed and small dark and round (Fig 80) Some idea as to prognosis and rapidity of progress of the disease in an individual case may be gained from the frequency of mature forms in the sternal marrow The more chronic and slowly progressive cases tend to have a predominance of mature cells

Multiple Myeloma as Form of Leukemia Michael A Rubinstein (New York City) presents evidence that the generally accepted points of distinction between multiple myeloma and leukemia cannot be regarded as fundamental and that there is no sharp demarcation between the two diseases

There are often features of leukemia in multiple myeloma

(7) *Blood* 4 1049 1066 S pt mb 1949

was the most frequent complaint of patients in this series Pathologic fractures accounted for pain in some instances but in many others there was no obvious explanation and x rays failed to reveal any lesion in the skeletal structure in the region of the pain Weakness developed during the illness in all patients and was a major complaint of 23 on admission In 20 patients neurologic complications were present in 6 as the outstanding feature The multiple small circumscribed osteolytic lesions found in the bones on roentgen examination are the most typical and outstanding manifestation of the disease Diffuse osteoporosis is also a common but less striking manifestation but it is often overlooked

The cause of the bleeding tendency in multiple myeloma has not been adequately explained In none of the nine cases in which it was present was hemorrhage severe enough to affect the course The importance of hyperproteinemia and hyperglobulinemia in this disease has been repeatedly emphasized Rapid sedimentation rate autohemagglutination and unusual rouleaux formation which may be encountered in peripheral blood of multiple myeloma patients seem to be a function of or to be dependent on hyperproteinemia Though the electrophoretic pattern of plasma or serum is abnormal in most if not all cases of multiple myeloma electrophoretic studies cannot be considered an important diagnostic aid until the chemical structure of the proteins producing the abnormal patterns is clarified Elevated serum calcium is found in 30 50 per cent of cases but serum phosphorus is normal or low except when there is renal insufficiency Alkaline phosphatase is normal Renal complications are found in 50-70 per cent of cases

Hemoglobin below 12 Gm /100 cc and a red cell count below 4 000 000 was found in 43 cases in this series Anemia was slightly hypochromic as a rule The total leukocyte count was within normal limits in 40 cases and was above 10 000 in only 4 Differential count was normal in all but two cases In only one were plasma cells found in the peripheral blood stream One might expect to encounter plasma cells in peripheral blood far more frequently than is the case since such cells are found within vessels in the region of the tumor

Bone marrow aspiration in multiple myeloma has emphasized that although roentgen evidence of the disease may be

Cryoglobulin Present in High Concentration in Plasma of Case of Multiple Myeloma Cryoglobulins are the class of proteins in which precipitate on cooling of plasma and redissolve on warming Robert M Hill Stuart G Dunlop and Richard M Mulligan[8] (Univ of Colorado) report the case of a patient with multiple myeloma whose blood solidified quickly in the needle and syringe while it was being drawn even though large amounts of anticoagulant were used However when the syringe and needle were warmed this did not occur When 7 5 ml heparinized blood was kept at 37 40 C and centrifuged there was a 3 ml upper layer of apparently normal plasma a 2 8 ml middle clear almost water white layer and a 1 7 ml lower layer of cells On cooling the upper layer remained liquid but the middle layer congealed to a pearly white translucent solid On warming the middle layer became liquid After a whole blood transfusion separation into three layers never occurred though the whole blood or plasma solidified on cooling as before The urine was free from protein at all times

Viscosity of the patient s plasma was more than five times that of normal plasma at 38 C and rapidly increased to infinity at 32 C Separated cryoglobulin gave strong biuret xanthoproteic Millon and Acree Rosenheim reactions and a negative Molisch reaction Cholesterol ester crystals were obtained and probably represented a lightly bound lipid fraction of the protein molecule Micro Kjeldahl analysis showed an average of 15 13 per cent nitrogen content By microbiologic assay 10 amino acids were detected The amino acid pattern suggested a relation to beta or gamma globulins All of the analyses physical properties and behavior toward sodium sulfate fractionation of the cryoglobulin were compatible with its classification as a pseudoglobulin

Terminally total protein was 18 1 Gm per cent of which 9 8 Gm per cent was globulin This amount of globulin reflects the tremendous terminal metabolic activity of the neoplasm itself

Treatment of Multiple Myeloma with Urethane William J Harrington and William C Moloney[9] (Tufts College) treated 11 patients with multiple myeloma with urethane

(8) J L b & Cl Med 34 1057 1065 A gu t 1949
(9) C 3 253 271 M h 1950

In addition to the well known circumscribed tumor formation diffuse infiltration of the bone marrow also exists in multiple myeloma Cases of diffuse infiltration without evidence of circumscribed tumor formation are known Lack of circumscribed tumor formation does not rule out the possibility of *multiple myeloma Extraskeletal visceral myelomatous spread* involving the kidney spleen lymph nodes etc occurs in some cases of multiple myeloma Not only visceral organs but blood itself may be invaded by myeloma cells Although massive invasion of peripheral blood so as to produce the picture of plasma cell leukemia occurs rarely occasional myeloma cells may be found in concentrated smears (corresponding to the aleukemic forms of leukemia) even though they may be missed on routine examination Increased uric acid content of the blood and elevated basal metabolism characteristic of leukemia are frequently seen also in myeloma Though the accepted textbook view is that myeloma is a disease of older age isolated instances of myeloma in younger age groups including infancy have been observed Whereas in most cases symptomatology of multiple myeloma is due to tumor involvement of bones in a number of patients complaints are not referable to the osseous system and may be similar to those ordinarily found in leukemia

On the other hand there are often features of myeloma in leukemia Rare cases of leukemia have been reported in which only bone marrow was involved These rare forms would correspond to the usual forms of multiple myeloma limited to bone marrow and without visceral involvement Less uncommon is involvement of different bones in leukemia Lesions may take the form of tumors destruction and absorption of bone leading to fractures or periosteal elevations and arthritis Bence Jones proteinuria and hyperproteinemia admittedly typical of multiple myeloma have also been occasionally observed in leukemia Sometimes symptoms referable to bones and joints dominate the clinical picture of leukemia

Rubinstein concludes that the difference between myeloma and leukemia as far as the conventional distinguishing features are concerned is merely one of incidence what is rare in one disease *is common in the other and vice versa* Multiple myeloma is probably a leukemia of plasma cells ordinarily of aleukemic type

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Dosage was usually 3 6 Gm daily given orally Six patients apparently responded clinically and from the laboratory stand point Five patients died one of intercurrent disease Another patient was in an advanced stage of the disease and died within two weeks after start of urethane therapy Three pa tients received adequate doses of urethane but failed to re spond Because of immature characteristics of myeloma cells in the bone marrow and rapid clinical course these patients were considered to have an acute form of multiple myeloma Experience with urethane in myelogenous leukemia indicates that these acute forms will probably not respond to urethane whereas the drug may bring about effective remissions in the more chronic forms

Clinical improvement was striking All nine patients with bone pain were greatly relieved In the six patients with a good clinical response weight gain was a conspicuous finding and three patients showed striking improvement in hemo globin and red cell levels There were also reduction in ab normal serum proteins and suppression of myeloma cell pro liferation in the bone marrow No statistical validity can be attached to figures regarding length of survival in 11 cases However mean survival time for all 11 cases is 21 months and average survival time 25½ months These figures are already better than those recently reported in 55 cases followed from onset of symptoms to death

It has been pointed out that urethane may cause gastro intestinal disturbances and serious leukopenia Use of spe cially coated tablets in this study appreciably lessened the tendency to nausea and vomiting and frequent blood studies furnished warning of impending leukopenia Withdrawal of urethane and prophylactic use of antibiotics have prevented to date any serious sequelae to suppression of white blood cells

Urethane is not a cure for multiple myeloma and expe rience with many more cases will be necessary before its thera peutic usefulness can be adequately evaluated Nevertheless in a disease which has been so persistently resistant to all forms of therapy results of urethane administration to this group of patients suggest that multiple myeloma may be added to the growing list of neoplastic diseases that may be come subject to chemotherapeutic control

Treatment of Acute Leukemias of Childhood with Folic Acid Antagonists Eugene J Weber Felix E Karpinski Jr and Robert W Heinle[1] (Western Reserve Univ) treated 24 children with acute leukemia by administration of the folic acid antagonists aminopterin and A methopterin Hematologic or symptomatic improvement or both occurred in 20 When diagnosis was established intramuscular injection of 1 mg aminopterin daily was begun The drug was discontinued when toxic lesions occurred or hematologic depression was noted After an observation interval treatment was resumed 1 mg being given intramuscularly every second day If this was well tolerated and peripheral counts remained stabilized the patient was discharged to be observed in the clinic three times weekly Aminopterin was given on each clinic visit according to an arbitrary schedule generally depending on the leukocyte count (over 6 000/cu mm 1 mg 2 000 6 000/cu mm 0 5 mg and under 2 000/cu mm none)

Roentgen changes of the skeleton were seen in 13 children on initial examination Skeletal lesions developed in three others during treatment Four types were observed osteolysis radiolucent transverse bands osteosclerosis and subperiosteal new bone formation

All patients followed a similar hematologic course Initial response was depression of bone marrow with reduction of all elements normal and abnormal Nucleated cell count of the marrow regularly fell to 400 000 500 000/cu mm (normal for the method used 1 000 000 2 000 000/cu mm) Peripheral blood showed anemia and leukopenia This phase was concurrent with initial intensive therapy Megakaryocytes and platelets were decidedly reduced and bleeding tendencies occurred With discontinuance of the antagonist cellularity of marrow increased and normal cells returned in greater numbers The most normal marrow was found four to six weeks after therapy was instituted In several patients abnormal marrow cells dropped to less than 1 per cent of the total and peripheral blood studies were entirely within normal limits Despite continued therapy however the number of abnormal cells in marrow gradually increased Appearance of abnormal cells in peripheral blood was delayed often not occurring until more than 75 per cent of marrow cells were abnormal In a

(1) J P diat 36 69 78 J ry 1950

few patients a second and fatal hematologic depression oc curred after long continued therapy Terminal course of these patients was that of an aplastic anemia At autopsy it was pos sible to demonstrate severe hypoplasia of the marrow and frequently there was little or no evidence of leukemia

Toxic lesions observed in these patients were limited to mucosal ulcerations of the mouth (Fig 81) accompanied by some degree of fever Lesions were erythematous patches with an ulcerated necrotic center which ultimately healed with for



F g 81 —To ic lcer t o of t g a l l ps c nd y to a pt th apy (C urt y f W ber E J t l J Ped t 36 69 78 Ja y 1950)

mation of a heavy crust Attempts to hasten healing by ad ministration of crude liver extracts and folic acid were not *successful The most effective treatment consisted* of admin istration of sulfadiazine by mouth and topical application of an aqueous solution of gentian violet

Mechanism of action of folic acid antagonists is thought to be production of a folic acid deficiency However when three children who had attained hematologic and symptomatic re missions were placed on daily oral doses of 20 30 mg folic acid marrow peripheral blood and clinical course were un altered after three to four weeks indicating that the occur rence of relapse was not accelerated by administration of folic acid in this dosage

Although folic acid antagonists did not constitute a satis factory form of therapy for *leukemia they were more effec tive* than other forms of treatment

The final articles in thi section deal with the use of the so called nitrogen mustards There is now a new compound melamine which can be given orally and is said to be free from the side effects on the gastro intestinal tract of the older drugs As it is still in the stage of clinical trial its comparative efficiency remains to be established Our own view about these drugs i that they are chiefly u eful only when x ray cannot for one reason or another be employed Th se circumstances are defined in the following abstracts —Ed

Treatment of Malignant Disease with Nitrogen Mustard N B Kurnick Karl R Paley Mack H Fieber and D K Adler (Mount Sinai Hosp New York City) report results in 64 patients with malignant diseases treated with HN_2 Of these 24 had Hodgkin s disease 4 chronic lymphatic leuke mia 2 chronic myelogenous leukemia 10 lung carcinoma 2 Wilms tumor 1 breast carcinoma 1 anaplastic metastatic carcinoma 1 melanocarcinoma 8 lymphosarcoma 2 mycosis fungoides 1 chronic nonleukemic myelosis 3 reticulum cell sarcoma 1 spindle cell sarcoma 1 miliary tuberculosis 1 Boeck s sarcoid and 2 malignancy of undetermined nature All but eight were given HN_2 in the usually recommended dose of 0 1 mg /kg on each of four successive days the eight received 10 mg daily for four days Twenty patients received two to six such courses

Results in general agreed with those of other investigators Favorable results comparable with those obtained with radio therapy followed HN treatment in most cases of Hodgkin s disease Fever when present subsided dramatically by the third day Sense of well being and regression of lymphade nopathy were usually noted during the first post treatment week whereas hepatosplenomegaly receded during the second week Contrary to earlier reports striking reduction in spleen size was common In a few cases pain due to bone lesions re sponded satisfactorily One patient who had become resis tant to roentgen rays responded to HN and was subsequently sensitive to radiotherapy Relapses occurred in all cases in a few days to 10 months In most cases remissions became pro gressively shorter with successive courses of HN Chronic lymphatic leukemia lymphosarcoma mycosis fungoides and reticulum cell sarcoma showed variable responses Carcinomas were uniformly unresponsive except for one bronchogenic adenocarcinoma and one Wilms tumor One patient with chronic nonleukemic myelosis was dramatically benefited

(2) A I t M d 30 974 1003 M y 1949

with diminution in spleen size and restoration of normal blood picture No cures were observed However in one proved case of generalized Hodgkin s disease only one small splenic granuloma with degenerative changes could be found at autopsy Death was due to agranulocytosis and thrombocytopenia secondary to excessive therapy The almost complete suppression of granulomatous disease suggests the desirability of using maximal tolerated dosage The authors recommend that the therapy schedule be revised to provide for an initial series of closely spaced courses for maximal therapeutic effect perhaps to be followed by regularly spaced maintenance doses

Toxic reactions were the same as those previously reported and were thought to be unrelated to injection rate Nausea and vomiting occurred in almost all cases but was often milder with successive injections No appreciable relief was obtained with pyridoxine atropine teropterin® or sedation Numerous visceral function tests revealed no changes attributable to HN₂ therapy except the hemopoietic response Lymphopenia usually occurred between the third day of treatment and the second post treatment day Leukocyte counts below 3 000 occurred in almost every case with the minimal count 3 25 days after treatment (average 11 days) infection was rare even with counts below 1 000 Anemia secondary to treatment was noted only twice and thrombocytopenia was noted seven times with bleeding four times Hemotoxic effect was entirely unpredictable nor was its severity related to response of the primary disease Teropterin® had no effect in preventing the myelotoxic effect or in hastening recovery

HN therapy is of value in Hodgkin s disease occasionally in lymphosarcoma and mycosis fungoides and probably in nonleukemic myelosis but it is of no value in carcinoma In cases of widespread or inaccessible lymphomatous lesions in which roentgen therapy is not feasible HN is particularly useful Fever due to lymphomas responds much more regularly to chemotherapy than to irradiation In moribund patients the more rapid and occasionally dramatic effect of HN is advantageous Constrictive lesions of the great vessels or the spinal cord often respond more rapidly to the chemical agent than to roentgen rays Initial swelling of tumor tissue often seen after x ray therapy was not observed with HN

Radiotherapy remains the preferred treatment for readily accessible or localized lesions

Treatment of Lymphomas and Other Neoplastic Diseases with Nitrogen Mustard Louis K. Alpert Ezra M Greenspan



Fg 8 —Hodgk d E l g d m d t l lymph od bef HN the py (C t y f Alp rt L K. *et al* An I t. M d 3 393 43 M h 1950)

and Stanley S Peterson[3] review results in 52 patients with various lymphomas and other neoplastic diseases treated with HN at Walter Reed Hospital Favorable though temporary effects were observed in most of 27 patients with Hodgkin s disease 3 with giant follicular lymphoblastoma and 2 with lympholeukosarcoma (Sternberg) In patients with lympho

(3) A I t M d. 32 393 43 M h 1950

with diminution in spleen size and restoration of normal blood picture No cures were observed However in one proved case of generalized Hodgkin s disease only one small splenic granuloma with degenerative changes could be found at autopsy Death was due to agranulocytosis and thrombocyto penia secondary to excessive therapy The almost complete suppression of granulomatous disease suggests the desirabil ity of using maximal tolerated dosage The authors recom mend that the therapy schedule be revised to provide for an initial series of closely spaced courses for maximal therapeutic effect perhaps to be followed by regularly spaced maintenance doses

Toxic reactions were the same as those previously reported and were thought to be unrelated to injection rate Nausea and vomiting occurred in almost all cases but was often milder with successive injections No appreciable relief was obtained with pyridoxine atropine teropterin® or sedation Numerou visceral function tests revealed no changes attributable to HN therapy except the hemopoietic response Lymphopenia usu ally occurred between the third day of treatment and the sec ond post treatment day Leukocyte counts below 3 000 oc curred in almost every case with the minimal count 3 25 days after treatment (average 11 days) infection was rare even with counts below 1 000 Anemia secondary to treatment was noted only twice and thrombocytopenia was noted seven times with bleeding four times Hemotoxic effect was entirely unpredictable nor was its severity related to response of the primary disease Teropterin® had no effect in preventing the myelotoxic effect or in hastening recovery

HN therapy is of value in Hodgkin s disease occasionally in lymphosarcoma and mycosis fungoides and probably in nonleukemic myelosis but it is of no value in carcinoma In cases of widespread or inaccessible lymphomatous lesions in which roentgen therapy is not feasible HN_2 is particularly useful Fever due to lymphomas responds much more regu larly to chemotherapy than to irradiation In moribund pa tients the more rapid and occasionally dramatic effect of HN is advantageous Constrictive lesions of the great vessels or the spinal cord often respond more rapidly to the chemical agent than to roentgen rays Initial swelling of tumor tissue often seen after x ray therapy was not observed with HN

Although the most important toxic effects were observed in the hemopoietic system panhematopenia only occasionally limited treatment Development of moderate leukopenia was considered an indication of effective dosage Since leukopenia was usually of short duration white cell counts as low as 2 000/cu mm were not considered a contraindication to HN_2 therapy Thrombocytopenia and purpura was the most serious complication encountered

Nitrogen mustard therapy appeared to be most suitable in the following clinical types of Hodgkin s disease (1) wide spread involvement which cannot be treated adequately with x ray (2) lymphadenopathy with striking constitutional symptoms (fever weight loss etc) (3) fever without demon strable enlarged nodes (occult febrile type) (4) visceral involvement and (5) terminal cases which have become re sistant to roentgen therapy Radiation was the therapy of choice in patients with relatively localized disease in periph eral mediastinal or retroperitoneal regions obstructive lesions around the spinal cord biliary tract ureters or great vessels bone involvement and fibrosing Hodgkin s disease Figure 82 shows enlarged mediastinal lymph nodes with Hodgkin s disease before HN therapy There was complete shrinkage of hilar lymphadenopathy after one course Despite three additional courses (total dose 134 mg) mediastinal adenopathy recurred as illustrated in Figure 83

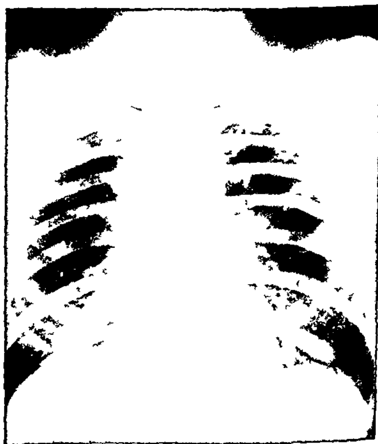
PURPURAS

The first two art cles in this section are general surveys of the hemor rhagic states and of thrombopenic pu pura respectively They should be studied in the orig nals for much that cannot be included in abstracts —Ed

Etiology and Management of Hemorrhagic Diatheses are discussed by Charles A Doan[4] (Ohio State Univ) When few or no blood platelets are found in blood of any patient with purpura study of bone marrow is essential to determine whether this deficit is secondary to bone marrow megakary ocytic inadequacy or excessive splenic demand (Fig 84) Generalized purpura is frequently the first sign of progres

(4) A I t M d 31 967 988 Decemb 1949

sarcoma reticular cell sarcoma chronic lymphatic leukemia subacute myeloid leukemia sarcoidosis and various carcinomas little or no significant benefit resulted even though varying degrees of tumor shrinkage were produced In only



F g 83—Recu r of m d t n l ad pathy n the ame pat t 18 m th fte HN th py was beg n F o of t t n t (t tal d 134 mg) were g e d r g th s ter al (Co rt y f Alpe t L K et l A I t Me l 3 393 43 Ma h 1950)

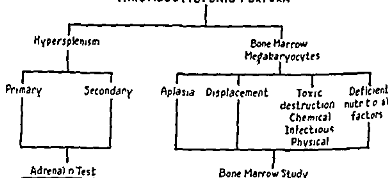
two patients was Hodgkin s disease adequately controlled for more than a year with repeated courses of HN alone In 17 patients x ray therapy was necessary to produce longer remissions than were obtained with HN_2

disappearance of all purpuric manifestations Toxic marrow destruction or inhibition may result from chemicals physical agents roentgen rays and radioactivity and infections Careful supravital study of fresh living marrow in thrombocytopenic purpura at once reveals clearly and unequivocally any specific damage to megakaryocytes which may be responsible for the circulating platelet deficit Vacuolated nuclei and cytoplasm with chromatin karyorrhexis and increased phagocytosis of specific cellular debris are unmistakable evidences of such toxic damage Elimination of the offending agent accompanied by supportive fresh blood transfusions permits regeneration of megakaryocytes Splenectomy in selected instances is followed by marrow recompensation

When peripheral thrombocytopenia has been found associated with clinical purpura and bone marrow studies not only fail to reveal cellular aplasia displacement damage or toxicity but actually reflect an excessive multiplication of megakaryocytes the more mature units showing active cytoplasmic platelet fragmentation in the living supravital preparations the conclusion is justified that despite the apparently uninhibited compensatory megakaryocytic hyperplasia the peripheral platelet demand is in excess of the available supply When the spleen is not demonstrably enlarged primary splenic thrombocytopenic purpura is the most likely diagnosis

The adrenalin test may reveal hypersequestration of platelets by a normal sized spleen indicative of a primary specific withdrawal or inhibition of circulating platelets in primary hypersplenic thrombocytopenic purpura (Werlhof s disease) When there is an obvious splenic enlargement with adrenalin test evidence of specific platelet hypersequestration and bone marrow shows only compensatory megakaryocytosis without myelophthisic or toxic marrow damage a hypersplenic syndrome secondary to some other disseminated constitutional disease must be considered Primary splenic Hodgkin s granuloma splenic Gaucher s disease chronic leukemic involvement of the splenic parenchyma by any cell type tuberculosis or tertiary syphilis of the spleen congestive splenomegaly secondary to myocardial decompensation acute splenic tumor of infectious etiology all have been associated with hypersplenic thrombocytopenic purpura Emergency splenectomy should be performed on exactly the same reasoning as for primary

sive marrow hypoplasia When on repeated studies of bone marrow obtained from the manubrium and the body of the sternum from selected spinous processes and from the crest of the ilium no megakaryocytes are found but there is definite evidence of a beginning marrow pancytopenia and when neither past personal history nor direct investigation reveals toxic environmental medicinal or bacterial factors primary hypoplasia with or without osteofibrosis or osteopetrosis mechanisms may be established In a certain proportion of such patients extramedullary hemopoiesis in spleen and liver



F g 84 (Courtesy of Doa C A Ann Int. Med 31 967 988 D c mber 1949)

may partially compensate for marrow hyperplasia In early stages with only moderate marrow hypoplasia splenectomy may be followed by a remission of months or years Replacement of fresh citrated blood transfusions is the treatment of choice for primary marrow aplasia Polycythemic donors have made particularly effective blood contributors Generous use of any or all of the presently known stimulatory and maturing factors for blood cells liver folic acid vitamin B_{12} etc have thus far failed to affect marrow regeneration in this type of patient

In certain naturally occurring circumstances in persons with food idiosyncrasies or gastrointestinal abnormalities concerned with disturbed digestion and absorption thrombocytopenic purpura on a deficiency basis secondary to general marrow hypoplasia may occur Correction of any specific deficiency is followed by regeneration of megakaryocytes and

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hypersplenism regardless of the known presence of serious disease elsewhere in the body

When normal or excessive numbers of platelets are found in circulating blood of patients with purpura immediate studies are indicated to differentiate between specific plasma and/or capillary defects It is now routine to determine pro thrombin plasma level in every patient showing any hemor rhagic tendency Low prothrombin levels cause purpura in hemorrhagic disease of the newborn in obstructive jaun dice in liver disease in persons on a low vitamin K diet and in patients with hyperperistalsis or other intestinal conditions preventing proper vitamin K absorption

Bleeding after extensive irradiation or nitrogen mustard administration has been attributed to excess of heparin or heparin like substances Protamine or toluidine blue dye are effective in controlling hemorrhage from these causes Recur ring if not constantly demonstrable abnormally prolonged coagulation time without thrombocytopenia warrants diag nosis of hemophilia Fresh whole blood fresh plasma or freshly frozen or lyophilized plasma from normal donors which contain antihemophilic globulin reduce the prolonged in vitro coagulation time as does plasma fraction I of Cohn available through the American Red Cross Afibrinogenemia occurs rarely as a congenital and usually familial disease and may be treated with fresh blood or plasma transfusions

Hereditary telangiectasis is of more cosmetic than hemor rhagic significance In hereditary pseudohemophilia there is inherent inability of the capillary wall to contract following injury leading to a prolonged bleeding time in a patient with nonthrombocytopenic purpura Fresh whole blood transfu sions produce the best therapeutic results

Possibility of anaphylactoid purpura may be elucidated by careful history and skin and dietary elimination tests Anti histaminic drugs are sometimes helpful or desensitization with histamine diphosphate or an autogenous urinary proteose concentrate may produce remission

Problem of Essential Thrombocytopenic Purpura is dis cussed by Charles F Stroebel Donald C Campbell and Albert B Hagedorn [5] The cause of this condition is not known Ac

(5) M Cl North Am ca 33 1027 1046 J ly 1949

cording to one view there is excessive destruction of platelets by the spleen Another view suggests that the spleen elaborates some substance which suppresses formation of platelets from the megakaryocytes The fact that splenectomy is of some benefit in this disease indicates that the spleen somehow plays a role in its mechanism The objection to the concept of hypersplenism is that splenectomy does not benefit all patients One might conclude that some cellular system such as the histiocytic plays a major role and that splenectomy is of value because it removes a large depot of histiocytes Microscopic study of the spleen reveals no consistent abnormal pattern Grossly the spleen is little if at all enlarged A third view points to capillary abnormality and suggests that thrombocytopenia occurs because of an excessive demand for platelets to close capillary defects The recent suggestion that blood of some patients with this disease and with certain other diseases associated with abnormal bleeding contains an excess of heparin like substance is still being investigated The role of allergic response also needs further study

Diagnosis depends on recognition of abnormal capillary fragility and thrombocytopenia and exclusion of known causes of these conditions Purpura is manifested by bright red to purple macules which later turn brown and fade because of disintegration of hemoglobin and absorption of hemosiderin Purpura is gross external evidence of a break in continuity of small blood vessels One of the simplest methods of producing purpura is with the tourniquet test in which capillaries of the forearm are distended by elevation of venous pressure to a level just above diastolic pressure The sphygmomanometer cuff is applied in the usual place Bleeding time is obtained by observing the time required for a small inflicted wound to stop bleeding If capillaries are normal the time usually does not exceed five minutes Periods beyond 10 minutes indicate abnormal capillaries Purpura is seen in many conditions not associated with thrombocytopenia Addition of thrombocytopenic to the diagnostic term depends on laboratory demonstration of reduction of platelets in circulating blood In essential thrombocytopenic purpura blood coagulation time is normal but the clot does not retract normally Clot retraction is thought to be a function of platelets

There are three general types of nonthrombocytopenic

purpura (1) Allergic purpura is seen in association with other manifest allergic disorders (2) Symptomatic purpura occurs in acute infectious diseases after snake bites and some times after ingestion of certain drugs e g belladonna co paiba iodides quinine mercurials bismuth and salicylates Purpuric manifestations are sometimes seen in advanced renal and cardiac disease Scurvy may also be classified as sympto matic purpura (3) Idiopathic purpura includes nonthrombo cytopenic purpuric bleeding from the gastrointestinal tract (Henoch s purpura) and the rheumatic purpura of Schönlein

Certain other nonthrombocytopenic hemorrhagic condi tions must also be distinguished In some persons bleeding from wounds may be excessive bleeding time prolonged and tourniquet test positive Purpura is not a prominent feature and platelet count coagulation time and clot retraction are normal This type of disease is called pseudohemophilia Ex clusion of other forms of nonthrombocytopenic bleeding dis ease involves recognition of the bleeding time in hemophilia fibrinopenia and hypoprothrombinemia

When purpura and thrombocytopenia occur other con ditions and agents which produce these manifestations must be excluded such as ingestion of certain chemicals (sedor mid® gold salts sulfonamides phenobarbital benzene nitro gen mustards dinitrophenol quinine ergot bismuth ar senicals and iodides) radiation therapy myelogenous and lymphocytic leukemia lymphoblastomas aplastic anemia and myelophthisic anemias caused by metastatic carcinoma and chronic intoxications Sternal aspiration is of value in exclud ing these diseases Thrombocytopenia is not infrequently seen in certain chronic diseases involving splenomegaly such as Gaucher s disease Felty s syndrome Banti s disease and Hodgkin s disease and in definite parenchymal hepatic disease

Review of the records of 99 women and 51 men with essen tial thrombocytopenic purpura showed that about 18 per cent of women noted menorrhagia at onset of menstruation as their first symptoms Onset was before age 40 in over two thirds of the patients Increased incidence of other diseases producing secondary thrombocytopenic purpura developing after age 40 should make search for the primary disease all the more rigorous in this age group A family history of bleeding disease was rare though there were three instances

of transient thrombocytopenic purpura in babies born of mothers with the disease

Of 59 adults treated by splenectomy 84 7 per cent had satisfactory immediate response 10 2 per cent were unimproved and 5 1 per cent died in the immediate postoperative period Of 26 adults not treated by splenectomy 42 3 per cent had an immediate spontaneous remission lasting at least six months 26 9 per cent continued to have purpura and 30 8 per cent died within three months of cerebral hemorrhage Of 20 children 90 per cent had a good immediate result after splenectomy whereas 10 per cent continued to have mild purpura Of 11 children who did not have splenectomy 73 per cent recovered spontaneously and 27 per cent continued to have purpura There were no deaths in either group Splenectomy is recommended but long time prognosis should be guarded because of possible recurrences Previous duration or character of the disease postoperative behavior size or histologic appearance of the spleen and postoperative platelet response give no sure clue as to the future course of the disease

Three Cases of Thrombocytopenic Purpura Occurring after Rubella with Review of Purpura Associated with Infections J F Ackroyd[6] observed three cases of thrombopenic purpura following rubella during an epidemic in the spring of 1940 All showed purpura and ecchymosis 3 11 days after onset Two patients recovered spontaneously but 1 died of cerebral hemorrhage nine days after onset When first observed there were too few platelets in the blood of all three patients to permit counting In the two survivors platelets had returned to normal 20 days later and initial capillary fragility had decreased One patient re examined six months later was entirely normal

Although only seven well authenticated and six doubtful cases of thrombopenic purpura after rubella have been reported the occurrence in less than six weeks of three cases is a high incidence This epidemic was characterized by an abnormally large proportion of cases in which other complications developed suggesting that it might have been due to an unusually virulent virus possibly one with an exceptional tendency to cause purpura Therefore in addition five cases of uncomplicated rubella in the same epidemic were studied

(6) Q rt. J M d 18 99 318 Oct be 1949

In these platelet count was usually low and capillary fragility high at onset of the disease returning to normal during convalescence changes in erythrocytes leukocytes bleeding and coagulation time were observed Degrees of thrombopenia and increased capillary fragility after infections of apparently equal severity varied strikingly from one patient to another Since these changes are known to occur in other acute infectious diseases and the incidence of purpura never appears to bear any relationship to severity of the disease it is concluded that degrees of thrombopenia and increased capillary fragility depend on susceptibility of the tissues of a patient rather than on intensity of the primary infection

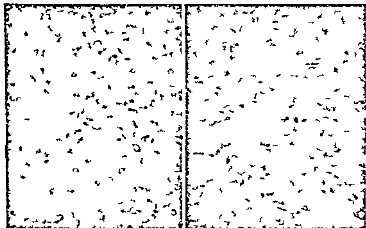
There are two striking facts in connection with this type of purpura (1) Purpura may occur in severe cases or may complicate very mild infections (2) Purpura may occur either during the acute stages of infection or during convalescence Different degrees of increased capillary fragility and thrombocytopenia appearing early in the disease and persisting for varying periods have been demonstrated in the cases reported here It seems probable that purpura occurring early represents a high grade of susceptibility In other patients the *existence of a symptom free period before onset of* purpura suggests the possibility of an allergic basis similar to that to which nephritis after streptococcal infections has been attributed

↓ The following article is important because it critically analyzes the mechanism of a type of purpura due to drug sensitivity —Ed

Mechanism of Reduction of Clot Retraction by Sedormid® in Blood of Patients Who Have Recovered from Sedormid® Purpura When sedormid® is added to blood of patients who have recovered from sedormid® purpura clot retraction is reduced and in some patients platelets are agglutinated These effects are not seen in blood of normal persons It is well known that if platelets are removed from plasma by centrifugation or by action of an antiplatelet serum clot retraction is reduced or even abolished It therefore seemed that action of sedormid® in reducing clot retraction might be due to an effect on platelets Since agglutination of platelets could not be demonstrated in blood of *all* patients in whom sedormid® caused reduced clot retraction however it seemed possible that this reduction was due to an effect of sedormid® on some

other part of the clotting mechanism J F Ackroyd (St Mary s Hosp Med School) added fibrinogen thrombin and platelets to different samples of the blood of patients who had recovered from sedormid® purpura and investigated action of sedormid® on clot retraction on the supposition that a normal clotting factor might replace one sensitive to sedormid® and so permit normal clot retraction in presence of the drug

Addition of fibrinogen to the blood of such patients or to normal blood reduced clot retraction When sedormid® and



F g 85 (l ft) —Ph tom g ph f pl tel t h pl m f m p ti t wh h d co d f om sedo m l® pu p t k n 0 m n t fte l w dd d Cl co ta me ou pl t l t

F g 86 (right) —Ph t m g ph f sam p t ent pl m tak 0 m t fte d l t w h t t d l t on f se] m l® l Platel t l t b p lly ll de g ly

(C t y f A k oyd J F Cl S 8 3 7 D mbe 1949)

fibrinogen were added to the blood of sedormid® sensitive patients reduction in clot retraction was greater than with either alone When thrombin was added to normal blood or to that of patients who had recovered from sedormid® purpura clot retraction was generally slightly reduced When thrombin and sedormid® were added simultaneously to the blood of such patients the thrombin lessened the reduction in clot retraction due to the sedormid ® but if sedormid® was allowed to act for

(7) Cl n. Sc. 8 235 67 Decembe 1949

five minutes before thrombin was added its action in reducing clot retraction was unimpaired There was thus no evidence that either fibrinogen or thrombin was concerned in action of sedormid® on clot retraction Thrombin seemed merely to accelerate coagulation and to prevent sedormid® from acting as completely as usual

In blood of patients who had recovered from sedormid® purpura observed microscopically during coagulation in the presence of sedormid® platelets were lyzed with abnormal rapidity (Figs 85 and 86) This presumably explains the action of sedormid® in reducing clot retraction because if platelets are removed from blood clot retraction is invariably abolished Excessive amounts of sodium citrate prevented the action of sedormid® on clot retraction apparently by protecting platelets from abnormal lysis by sedormid® during coagulation

Addition of normal platelets to normal blood or to the blood of sedormid® sensitive patients did not affect clot retraction Addition of normal platelets to the blood of a sedormid® sensitive patient to produce a final concentration of about 140 000/cu mm of added platelets did not improve clot retraction in presence of sedormid® though this concentration of platelets is sufficient to restore normal clot retraction to the plasma after its clot retraction had been abolished by centrifuging out the platelets If normal platelets were added to the platelet free plasma of patients recovered from sedormid® purpura and the plasma was subsequently clotted in the presence of sedormid® platelets were lyzed abnormally rapidly and clot retraction was greatly reduced If platelets of sedormid® sensitive patients were added to normal platelet free plasma which was then clotted in the presence of sedormid® platelets were not lyzed abnormally rapidly and clot retraction was normal If excessive amounts of platelets were added to a sensitized person s plasma which was then clotted in presence of sedormid® not all the platelets were abnormally lyzed because the drug and those remaining were able to promote normal clot retraction If a sufficiently large excess of platelets was added to whole blood action of sedormid® on clot retraction was entirely abolished

The author concludes that sedormid® reduces clot retraction in the blood of patients recovered from sedormid® pur

pura by causing lysis of platelets during coagulation this is the only factor involved Platelet lysis results from action of *some factor in the plasma and is not due to any peculiarity of* the platelets themselves

↓ The next three articles indicate the trend of important recent evidence to the effect that platelet deficiency causes a coagulation defect Thi ı rarely demonstrable by the crude technic of the coagulation test but none theless is clearly shown by the defective prothrombin consumption in the method devi ed by Quick —Ed

Coagulation Defect in Thrombocytopenic Purpura Nor mal coagulation time observed in thrombocytopenic purpura has always puzzled students of coagulation and has led many to conclude that coagulation is not disturbed in this disease Recently evidence however shows that coagulation time may not always be a reliable measure of true coagulability It has long been recognized that in hypothrombinemia the coagula tion time determination is much too insensitive to serve as a guide for estimating severity of prothrombin deficiency As a result of development of the prothrombin time determination rapid progress both clinical and theoretical ensued in the group of diseases in which prothrombin deficiency occurs With development of the prothrombin consumption time (serum prothrombin time) determination which measures quantitatively the factors responsible for activation of pro thrombin a new approach is offered for study of hemorrhagic diseases due to coagulation defects which are not in the pro thrombin complex i e diseases in which prothrombin time is normal

Absence of clot retraction which is characteristic of se vere thrombocytopenic purpura should no doubt be consid ered a coagulation defect Although it is recognized that clot retraction depends on intact platelets a quantitative correla tion between number of platelets and speed and degree of clot retraction was difficult to make until introduction of sili cone (Dri film) which made it possible to secure and keep na tive plasma with a minimum of platelet lysis

Armand J Quick Jacob N Shanberge and Mario Stefa nini[8] (Marquette Univ) correlated prothrombin consumption (obtained with the aid of silicone coated glassware) with the quantitative estimation of clot retraction and the platelet

(8) J Lab & Cl n. M d 34 761 767 J e, 1949

count of whole blood and of normal human native plasma from 20 normal adults and applied these findings to clinical thrombocytopenic purpura

In thrombocytopenic purpura delayed clot retraction and poor prothrombin consumption closely paralleled the low platelet count Prothrombin consumption time and speed of clot retraction simultaneously and promptly returned to normal as platelet count increased and clinical condition improved Platelet count prothrombin consumption and clot retraction responded quickly to splenectomy in one case of idiopathic thrombocytopenic purpura

The prothrombin consumption test supplies the first strong evidence that a coagulation defect is present in thrombocytopenic purpura The test offers a new measure of platelet activity which is postulated to be that of activating plasma thromboplastinogen Clot retraction likewise is a measure of intact platelet activity When the test is carried out on native plasma it has quantitative significance since the beginning and completion can be accurately determined by direct visual observation and no correction is required for cell volume

Factor in Serum Which Accelerates Conversion of Prothrombin to Thrombin Its Relation to Coagulation Defect of Thrombocytopenic Blood The exact role of the platelet in blood coagulation is the subject of considerable controversy Although thrombocytopenic plasma exhibits retarded coagulation a prolonged clotting time is rare in thrombocytopenic purpura This has been explained by the theory that even in severe thrombocytopenia sufficient thromboplastin is elaborated to produce normal coagulation The hemorrhagic manifestations of thrombocytopenic purpura have generally been ascribed to a great reduction in blood platelets to capillary dysfunction or to inadequate clot retraction rather than to abnormalities in coagulation itself

Benjamin Alexander and Andre de Vries[9] (Boston) present observations which indicate that coagulation of thrombocytopenic blood is profoundly disturbed In a previous article an agent in serum was described which accelerates conversion of prothrombin to thrombin in presence of thromboplastin plus calcium The agent serum prothrombin conversion accelerator (SPCA) is measured by the enhancement in per

(9) Blood 4 747 751 Jun 1949

cent of the prothrombin activity of normal oxalated plasma induced by the admixture to it of serum obtained from the blood in question one hour after coagulation Before the test the serum is oxalated then incubated for one half hour to inactivate thrombin

Ten subjects with thrombocytopenic purpura were studied All had platelet counts below 100 000/cu mm Mean SPCA activity was 33 per cent in contrast to 99 per cent for 95 normal subjects Residual serum prothrombin activity averaged 50 per cent compared with 6 per cent for normal persons No strict correlation was evident between bleeding time or platelet count and SPCA or residual serum prothrombin activity although subjects with the highest platelet counts seemed to have the highest SPCA activities Coagulation times of most of the patients were within normal range That the clotting times were essentially normal in these patients despite the clotting defect reflects the lack of sensitivity of this test Addition of normal platelets or thromboplastin corrected the observed abnormalities in SPCA and residual prothrombin activity In one subject the clotting defect persisted despite temporary remission of the thrombocytopenia consequent to splenectomy

Observations on Coagulation Defect in Thrombocytopenic Purpura While utilizing small amounts of heparin for prolonging coagulation of blood by the method of Waugh and Ruddick T Lyle Carr and Willis M Fowler[1] (State Univ of Iowa) noted that some patients who were actively bleeding had an augmented reaction to heparin

TECHNIC—Nine Wassermann tubes are used Tube 1 remains empty until blood is added and tube 2 contains 0 5 cc of 0 9 per cent normal saline Serial dilutions of heparin in 0 5 cc saline are added to the remaining seven tubes so that tube 3 receives 0 1 unit heparin tube 4 receives 0 2 unit heparin and so on until tube 9 receives 0 7 unit heparin To each tube is added 1 cc blood and the time which elapses from the moment blood is first seen in the withdrawal syringe until coagulation occurs is the end point in that particular tube

When the Waugh Ruddick test was performed on 30 normal subjects coagulation time in tubes 1 and 2 which contained no heparin varied from 4 to 12 minutes A gradual increase in time required for coagulation was found as greater amounts of heparin were encountered Coagulation ultimately

(1) J Lab & Cl Med 34 12 7 1 37 September 1949

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(9) Blood 4 747 751 Ju 1949

This reaction is not like that produced by intravenous in jection of commercial heparin Increased susceptibility of thrombocytopenic blood to heparin apparently is not due to an increased amount of circulating heparin like substance

Adhesiveness of Blood Platelets in Thromboembolism and Hemorrhagic Disorders Measurement of Platelet Adhesives by Glass Wool Filter Because of the possibility that blood coagulability is related not only to the number of circulating platelets but also to their adhesiveness many methods have been devised to study platelet adhesiveness Sylvan E Moolten and Leo Vroman (New Brunswick N J) devised a method in which a wick of braided glass wool i used as an absorbing filter for separation of adhesive from nonadhesive platelets in citrated blood thus making possible enumeration of their relative proportions in the total platelet count

TECHNIC —Commercial glass wool is drawn into three strands of equal size and worked into a loose braid 0 5 1 cm thick A segment 6 7 cm long is cut and split a short distance at one end to provide three supporting arms by which the braid is suspended vertically in a silicone coated test tube of 2 cm internal diameter The arms are secured over the rim of the tube by an elastic band The filter is readied for use by moistening it with 1 5 ml physiologic saline covering the upper end with a loose fitting Bakelite cap to prevent evaporation and warming it to 37 C Blood 1 8 ml is quickly drawn from the subject s vein into a silicone-coated syringe containing 0 2 ml of 3 8 per cent sodium citrate solution mixed and transferred to a silicone coated collecting tube A prefiltration platelet count is made immediately Ten minutes after the blood is drawn 1 ml is permitted to drip into the glass wool as quickly as possible without overflow or leakage Thirty second later the blood in the braid is washed through with 8 ml of chilled eluting fluid consisting of 1 part of 3 8 per cent sodium citrate solution added to 9 parts of physiologic saline cooled before use to about 5 C The washed braid is removed the filtrate mixed well and a postfiltration platelet count done The sample is drawn into a white cell counting pipet to the 0 5 mark and diluted to the 11 mark with formalinized citrate solution (The prefiltration platelet count is made by drawing the sample into a red cell counting pipet to the 0 5 mark and diluting to the 101 mark with the same solution) After the sample is shaken standard hemocytometer chambers are filled with the respective cell suspensions and permitted to settle Counts are made of the red blood cells in 5 small squares and of the platelets in 25 small squares When their number appears significantly less than normal platelets are enumerated in five large squares and the total divided by 5 Data for each sample (filtered and unfiltered) are charted as fol

(2) Am J Cl P th 19 701 709 Augu t 1949

occurred in 40 90 minutes In no instance was blood rendered incoagulable under these conditions

When the Waugh Ruddick test was performed on 15 patients with bleeding tendencies associated with primary or secondary thrombocytopenia coagulation time was essentially normal in the first two tubes which did not contain heparin but was decidedly prolonged in the remaining tubes containing serial dilutions of heparin Fluctuations were noted in speed of coagulation in individual patients from time to time when there was no significant change in number of platelets but when there were active clinical hemorrhagic tendencies the increased sensitivity to heparin was always present *Variations in Waugh Ruddick test results more nearly* paralleled clinical manifestations of hemorrhage than did the platelet level In these patients coagulation required 45 100 minutes in the presence of 0 1 unit heparin and in many instances blood was incoagulable in the fourth tube and in all subsequent dilutions These results show that coagulation time in such patients is normal in the absence of heparin but is decidedly increased with even small amounts of heparin and the blood is easily rendered incoagulable

In four of seven patients with thrombocytopenia administration of protamine sulfate and toluidine (1 4 mg/kg body weight) apparently shortened coagulation time in tubes containing 0 1 and 0 2 unit heparin and occasionally in the tube containing 0 3 unit heparin but had no effect on tubes containing a higher concentration This suggests that protamine in the blood stream was sufficient to neutralize 0 1 0 3 unit heparin but not larger amounts In two patients protamine sulfate and toluidine had no demonstrable effect and in the remaining patient the material was given concomitantly with a spontaneous remission

Waugh Ruddick test was done on five patients before and after splenectomy In four operation brought about complete remission by clinical and laboratory standards In all these patients Waugh Ruddick test results also returned to normal In the fifth patient operation was followed by an immediate but moderate rise in platelet count and a normal Waugh Ruddick curve Two months later cutaneous hemorrhages had reappeared platelet count had dropped and the Waugh Ruddick curve was again prolonged

bleeding time normal clotting time increased capillary fragility and poor clot retraction The diagnosis of thrombasthenia or pseudohemophilia was justified since in this syndrome platelet count is usually normal bleeding time is variable clotting time of venous blood may be normal or increased clot retraction is usually normal but may be poor and capillary fragility may be normal or strikingly increased Absence of a bleeding tendency in the family does not exclude this interpretation Other data also were like those found in thrombopenic purpura namely high residual serum prothrombic activity and prolonged recalcification time Since addition of normal platelets to plasma from the patient rectified the clotting defect and conversely addition of platelets from the patient to normal plasma deprived of its platelets did not correct the induced abnormality it must be concluded that the patient s platelets were inherently defective and unable to function normally Addition of normal platelets to thrombopenic blood similarly corrects the clotting defect Thus except for the normal number of platelets blood from the patient was indistinguishable from thrombopenic blood

Platelet count in this patient later dropped to thrombopenic levels suggesting a possible relation between thrombasthenia and idiopathic thrombopenic purpura It is suggested that idiopathic thrombopenic purpura is sometimes preceded if only for a short time by abnormal platelets that are removed from the circulation The following method for measuring functional capacity of platelets is suggested

Technic —The platelets are added to normal plasma deprived of its platelets with precautions against platelet breakdown The mixture is recalcified and residual serum prothrombic activity determined Normally no prothrombin should be demonstrable The amount of prothrombin remaining in the serum i a measure of thromboplastin evolving from the platelets since all other clotting factors important in prothrombin conversion will have been provided or adequately controlled

Disseminated Arteriolar and Capillary Platelet Thrombosis Morphologic Study of Its Histogenesis Ira Gore[4] (Armed Forces Inst of Pathology Washington D C) reviews five cases of disseminated arteriolar and capillary platelet thrombosis Significant clinical features are insidious onset of vague nonlocalizing symptoms fever purpura anemia and

(4) Am J P th 26 155 175 J ry 1950

lows (1) red blood cells/5 small squares (2) platelets/25 small squares × 2 (3) total red blood cells corrected for added citrate (4) total platelets corrected for added citrate (5) red blood cell platelet ratio (6) adhesive index—value for red blood cell platelet ratio of filtered sample — that of the unfiltered sample Using the empirically found adhesive index of 0 7 as representing zero ad hesiveness numerical approximation of the number of adhesive platelets may be made by the following calculation nonadhesive platelets = total platelets — adhesive index + 0 3 adhesive plate lets = total platelets — nonadhesive platelets

The normal range of adhesive platelet count was found to be between 60 000 and 110 000 platelets/cu mm and the ad hesive platelet count in individual normal persons was found to vary less from time to time than the total platelet count The glass wool filter method of measuring platelet adhesive ness is relatively simple and can be readily applied clinically as an aid to detection of predisposition to thrombosis and re lated conditions

[It is possible that as also suggested by Wiener purpura occurring with relatively normal platelet counts may be due to defective platelet func tion This is also suggested by the following report of defective prothrom bin consumption in the blood of such a patient —Ed]

Thrombasthenia and Thrombocytopenic Purpura Report of Case Demonstrating Qualitative and Quantitative Inade quacy of Platelets is made by Benjamin Alexander and Greta Landwehr[3] (Harvard Univ) Although the role of platelets in the hemostatic mechanism is not entirely understood it is clearly established that reduction in platelet number is asso ciated with hemorrhagic phenomena prolonged bleeding time abnormal clot retraction and disturbed capillary retractility The degree of thrombopenia necessary to induce clinical and laboratory manifestations of purpura varies from patient to patient suggesting that qualitative differences in the platelets are important Furthermore existence of normal platelet counts in cases which have many features commonly asso ciated with thrombopenic purpura indicates that the quality of platelets in these patients may be poor In the case ob served such aberrations in platelet function actually occurred

The patient a man aged 40 had normal platelet counts early in the disease Nevertheless the following salient clini cal manifestations of thrombopenic purpura were present bleeding into the skin and from mucous membranes increased

(3) New Engl d J Med 41 965 968 Dec 15 1949

sues This seemed to be the reverse of what would be anticipated if the lesions were secondary to spontaneous agglutination in the circulating blood On the other hand when a section included an appreciable length of an involved vessel propagated platelet thrombi covered by a sleeve of hyperplastic endothelium were often observed The proliferating plump investing endothelial cells contrasted sharply with the flat tenuous lining of the occluded vessel and indicated an origin from a portion of the vessel not always in the plane of the tissue section Careful search revealed focal lesions of arterioles and capillaries on which platelet thrombi formed and from whence they grew along the length of the vessel

These focal lesions termed prethrombotic were rare The lesion consisted of a segmental accumulation of hyaline material beneath the endothelium of a capillary and between the endothelium and musculature of an arteriole (Fig 87) In focal areas swelling of this homogeneous substance bulged both into the vessel lumen carrying with it the overlying endothelium and externally producing a defect in the vessel wall Although the nature of this change cannot be established by ordinary histologic technic this swelling of the hyalin can best be explained by imbibition of fluid from circulating blood At any rate the swelling evidently progressed until there was a break in the overlying endothelium whereupon platelets accumulated rapidly to cover the defect Presumably the small caliber of vessels involved limited access of antithrombic substances so that propagation of the thrombus often occurred Reactive endothelial proliferation apparently started promptly at the attachment of the thrombi and tended to encompass them The resulting lesions were most frequently seen at autopsy

This syndrome differs both clinically and pathologically from any of the well established disease entities but has been described by several authors notably Moschowitz and Baehr and his associates

↓ The following article is a critical analysis of the effects of splenectomy which contributes much to our understanding by separating the immediate and nonspecific effects on bleeding time and capillary fragility from the later and more specific effect on platelet levels —Ed

Idiopathic Thrombocytopenic Purpura H N Robson

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(5) Q t J M d 18 79 97 Oct 1949

a rapidly progressive fatal course in which severe nonlocaliz ing mental and neurologic signs are prominent Tests of the clotting mechanism demonstrate increased bleeding time and defective clot retraction coagulation time is usually normal Capillary fragility is increased

At autopsy widespread purpura was present in all five cases appreciable splenomegaly was observed in three In other respects gross postmortem findings were nondescript

Platelet thrombi occluding capillaries and arterioles were the most striking microscopic features in all tissues examined



F g 87—A te l n the s b t n e f th p n F al b dothel al c m l t f hy l h a t g th p th mb t c l s o R d d f m × 395 (C tesy of Go e I Am J P th 26 155 175 Jan y 1950 f m A m d Fo c s Inst of P th logy cc n 113583)

Though the structure of thrombi could not be ascertained when they were compact and formed an amorphous or granu lar mass individual platelets could be seen in more loosely agglutinated portions Plugs of platelets obtained by centri fuging normal human blood presented similar morphologic features and staining reactions when they were fixed em bedded and sectioned in the same fashion None of the venules appeared to be involved Though most lesions at autopsy were relatively recent there was usually a small number of organ izing and organized occlusions which led to the inference that platelet thrombosing was episodic and that lesions occurred in crops

A paucity of platelet thrombi in lung capillaries and liver sinusoids was striking compared to their number in other tis

sues This seemed to be the reverse of what would be anticipated if the lesions were secondary to spontaneous agglutination in the circulating blood On the other hand when a section included an appreciable length of an involved vessel propagated platelet thrombi covered by a sleeve of hyperplastic endothelium were often observed The proliferating plump investing endothelial cells contrasted sharply with the flat tenuous lining of the occluded vessel and indicated an origin from a portion of the vessel not always in the plane of the tissue section Careful search revealed focal lesions of arterioles and capillaries on which platelet thrombi formed and from whence they grew along the length of the vessel

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Idiopathic Thrombocytopenic Purpura H N Robson[5]

(5) Q J M 18 279 297 Oct 1949

(Univ of Edinburgh) investigated 19 cases of idiopathic thrombocytopenic purpura with regard to changes in bleeding time capillary resistance and platelet counts before during and after splenectomy *Similar observations were made on a* control series of 13 patients on whom splenectomy was carried out for other conditions and 7 patients undergoing other abdominal operations Megakaryocytes in bone marrow were studied before and after operation

Splenectomy in cases of idiopathic thrombocytopenic purpura was associated with a sequence of changes in bleeding time capillary resistance and platelet counts Repeated observations made at short intervals during operation revealed that bleeding time began to decrease at or immediately after ligation of the splenic pedicle and continued to fall reaching normal levels 12 100 minutes from the time of initial skin incision Similarly capillary resistance improved reaching normal levels in 12 360 minutes and thereafter continued to increase so that after 1 192 hours a negative pressure of at least 500 mm Hg was usually necessary to produce one or more petechiae Platelet counts were altered much more slowly usually reaching normal levels in ½ 4 days Results of observations on control groups indicated that these changes were brought about initially by a nonspecific effect of operative interference followed by the effect of removal of the spleen

In 16 of the 19 cases recorded observations were made after discharge from the hospital at 3 months after splenectomy in most cases and again at varying periods from ½ to 14 years Fourteen of the 16 patients had remained clinically well despite the fact that only 6 showed entirely normal results in all three tests bleeding time capillary resistance and *platelet count There was a considerable reversion to hema*tologic abnormality after the dramatic improvement immediately after splenectomy Yet bleeding recurred in only 2 of the 16 Of 12 patients tested three months after splenectomy 8 already showed one or more abnormal results by tests and no evident subsequent improvement On the other hand normal results achieved by the remaining four patients at the end of three months were sustained In idiopathic thrombocytopenic purpura final effects of splenectomy cannot be accurately assessed before three months after operation

There was no increase in primitive forms of megakaryocytes in bone marrow in cases of idiopathic thrombocytopenic purpura Platelet formation however was diminished and this was alleviated by removal of the spleen

It is uggested that the cause of idiopathic thrombocytopenic purpura lies in production by the spleen and other reticuloendothelial tissue of some factor which alters the state of capillaries and also reduces platelet formation from megakaryocytes Removal of the spleen may bring about a complete or partial reversal of these changes with consequent variation in clinical results

BAL Treatment of Thrombocytopenic Purpura Beneficial effect of BAL in treatment of poisoning by heavy metals (mercury lead copper gold) is now well established In such cases BAL is thought to compete with heavy metals for sulfhydryl groups with which the heavy metals combine to become active H Honkapohja[6] (Univ of Helsinki) reports a case in which blood complications due to gold therapy were treated with BAL

Man 53 was given sodium gold thiomalate for two months because of tender swelling of the distal interphalangeal joints After treatment he complained of continuous lassitude and three months later purpuric areas appeared on both thighs and bleeding from the gums occurred Platelet counts were 40 000 and 43 000 He was hospitalized with a diagnosis of thrombocytopenic purpura and osteoarthritis

BAL was given in doses of 1 7 cc every 4 hours for 48 hours then 1 7 cc twice daily for 7 days As soon as there was a decrease in thrombocyte count BAL admini tration was resumed During therapy gold excretion in urine increased 40 times and thrombocytes increased in number The tourniquet test progre sively gave less positive results and bleeding phenomena ceased There were no manifest signs of BAL toxicity Total dosage was 74 8 cc The patient was followed for over six months and the number of thrombocytes remained over 100 000

COAGULATION DEFECTS

The first article by Soulier seems to us very important. Through comparison of the results of the prothrombin consumption test of Quick performed on the venous and capillary blood a convenient method of measuring effects due to tissue juice or tissue thromboplast n appears

(6) A med. t Fenn 38 33 37 1949

to have been devised Recent studies by Tocantins likewise indicate a deficiency of such substances in hemophilic tissues thus perhaps for the first time permitting an understanding of the striking tendency to extensive bleeding into tissues in that disorder Other articles follow which unfortunately for the clinical reader are necessarily concerned with various types of special laboratory studies However even if therapeutic progress is not outstanding significant knowledge concerning blood coagulation is coming from several clinics and laboratories We should like to pay tribute especially to the continuing contributions of Quick and his associates Over a period of years his instinct for physiologic analysis of the system with as little alteration as possible has yielded valuable results Progress has recently been powerfully aided by the use of silicone introduced by Jacques —Ed

Study of Prothrombin Consumption Practical Interest for Diagnosis of Hemorrhagic Diseases, Study of 89 Cases For two years J P Soulier[7] (Paris) has been studying prothrombin consumption in every case of hemorrhagic disease under his observation The method used can be applied to serum from venous blood and from capillary blood The difference between the two serums is that capillary blood contains some admixture of tissue juice this addition of thromboplastin in physiologic amount increases prothrombin consumption Comparison of the two serums is useful for diagnosis

TECHNIC —Venous and capillary blood (0 5 ml) are obtained and kept for four hours in a water bath at 37 C then centrifuged to collect the serum To 0 1 ml undiluted serum is added 0 1 ml of standard thromboplastin and the mixture is incubated in the water bath for exactly 60 second This period is long enough for complete conversion of prothrombin and too short to permit the different antithrombic activities of serum to affect the clotting time At the precise moment (60 seconds) 0 2 ml standard fibrinogen is added and clotting time recorded The method can be used in the same way on serum from clotted plasma results being parallel to those obtained with whole blood

Study of 17 normal subjects showed that normal prothrombin consumption time is over one minute for venous blood and over three minutes for capillary blood Study of 27 hemophiliacs revealed that prothrombin consumption times for venous or capillary blood or recalcified plasma were between four and six seconds and always less than eight seconds

Eight patients were referred with inaccurate diagnoses of hemophilia Three had hypoprothrombinemia as a result of dicumarol® intoxication Consumption time was over three minutes which was to be expected since the small amount of

(7) A ta med Sca d n v 137 1 14 1950

prothrombin was entirely consumed during coagulation Pro thrombin consumption was normal in four patients with Willebrand Jurgens syndromes (hereditary capillary defect with increased bleeding time normal platelets capillary re sistance clot retraction and clotting time) One heparinized patient with a clotting time of 85 minutes had a consumption time of 72 seconds

In three patients with an anticoagulant in the circulating blood consumption time was as short as in hemophilia How ever prothrombin consumption in a mixture of pathologic and control plasmas was quite different In hemophilia nor mal plasma corrected the consumption deficit In the presence of an anticoagulant pathologic plasma affected consumption of normal plasma and the mixture behaved like hemophilic plasma

In 31 cases of thrombopenia prothrombin consumption was impaired This finding was remarkable since clotting time did not reveal the profound disturbances of the first stage of coagulation In all cases prothrombin consumption time in serum from venous blood was always below 18 seconds In serum from capillary blood consumption time was always longer and often as long as in normal blood In other words in thrombopenia prothrombin consumption is le s defective than in hemophilia In capillary blood thromboplastin from tissue juice may more or less completely correct the deficiency observed in venous blood The prothrombin consumption de fect appears to be as important as clot irretractability for as certaining the presence of thrombopenia

Various other hemorrhagic syndromes were studied The prothrombin consumption time permitted division of these syndromes into a group with abnormal consumption time and one with normal consumption time thus permitting diagnosis of isolated vascular defect

Soulier concludes that prothrombin consumption time is a much more sensitive test than clotting time Normal clotting time is compatible with incomplete consumption of prothrom bin It was previously known that plasma prothrombin must be reduced below 20 or 30 per cent for clotting time to be de layed It is now known that if 100 per cent of prothrombin is present in plasma clotting time is delayed only when less than 30 per cent of the prothrombin is consumed In hemo

philia in which prothrombin consumption is usually below 30 per cent for both venous and capillary blood clotting time is greatly delayed and hemorrhages are very severe since tissue juice cannot correct the defect In thrombocytopenia prothrombin consumption averages between 30 and 60 per cent Clotting time therefore remains within normal limits Because the clotting defect is more or less corrected by tissue juice spreading hematomas are not observed as in hemophilia but rather petechiae ecchymosis and mucous membrane hemorrhages due to the capillary fragility and nonformation of thrombus These studies suggest the possibility of making a correct diagnosis of hemophilia with capillary blood

Significance of Different Methods for Prothrombin Estimation and Their Relative Values are discussed by John H Olwin[8] (Univ of Illinois) The methods of estimating prothrombin are at present bioassays and to understand them knowledge of the mechanism of blood coagulation is essential Blood clots in two stages In the first stage prothrombin in the presence of thromboplastin prothrombin accelerator and calcium is converted to thrombin In the second stage thrombin converts fibrinogen to fibrin Variation in these and other factors may influence the normal physiologic clotting of blood

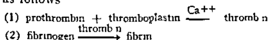
Methods used for measuring prothrombin are for the most part based on the so called one stage or two stage method The one stage test is not a measure of prothrombin in that it leaves uncontrolled a number of factors other than prothrombin and allows the two phases of clotting to go on concurrently It is rather a measure of the over all clotting activity of blood under certain specific conditions It is a more accurate gauge of the likelihood of bleeding in a patient than is the two stage test From study of over 350 patients on dicumarol® therapy Olwin found that according to the one stage method plasma prothrombin may drop to below 10 per cent without evidence of bleeding Of these 350 patients 109 at one time or another during therapy had a prothrombin level below 10 per cent and of these only 35 had bleeding in some form Other factors may compensate for a prothrombin deficiency thus acting as a safeguard and this safety factor will be registered by the one stage test The two stage method on the other hand by controlling most of the coagulation and

(8) S g Gyn & Ob t 90 4 3 4 9 Ap 1 1950

anticoagulation factors and by taking into consideration the two stages by which blood clots is a more accurate measure of available prothrombin The chief objection to it is that it is difficult to perform However once the required setup is obtained performance is neither difficult nor excessively time consuming

Though it would seem to follow that the most accurate of the methods for estimating prothrombin would be the most valuable one in all instances this is not necessarily true In some cases the chief concern is whether or not bleeding will occur during or after surgery and in such cases the one stage method is a better estimate of the safety factor than is the two stage This is generally true in all conditions in which information is desired as to the likelihood of bleeding from prothrombin deficiency In conditions in which an accurate prothrombin estimate is important i e suspected liver damage the two stage method is preferable Olwin has found the one stage method more useful for control of heparin therapy For dicumarol® therapy since efforts are directed toward control of the single factor prothrombin the two stage method is the one of choice Understanding of what each method represents is of prime importance in selection of the particular test needed and in interpretation of results

Two Stage Procedure for Quantitative Determination of Prothrombin Concentration, with detailed directions for preparation of reagents is described by Arnold G Ware and Walter H Seegers[9] (Wayne Univ) The only known way to identify prothrombin is to convert it to thrombin which is readily recognized by its property of changing fibrinogen to fibrin Equations for the reactions involved are generally written as follows



(1) prothrombin + thromboplastin $\xrightarrow{Ca^{++}}$ thromb n

(2) fibrinogen $\xrightarrow{\text{thromb n}}$ fibrin

When estimating prothrombin by two stage methods these reactions are completed one at a time Conversion of prothrombin to thrombin is first allowed to take place and then the second reaction is utilized to measure the amount of thrombin formed

It is now generally accepted that there is a factor in nor

(9) Am J Cl P th 19 471 48 M y 1949

mal plasma other than prothrombin or thromboplastin which affects the first reaction of clotting The authors refer to this factor by the term Ac globulin (accelerator globulin) Quantity of Ac globulin normally found in human plasma is sufficient to provide a maximal thrombin yield in analyses for prothrombin by the two stage procedure However if the amount of Ac globulin is much below normal the two stage analysis may indicate a false low prothrombin titer For this reason it has been necessary to modify the two stage method in order to assure a maximal yield of thrombin when Ac globulin is low or absent This is done simply by supplying an adequate amount of Ac globulin during the analytic procedure Diluted bovine serum fresh or carefully preserved in the cold is used for this purpose With this modification the two stage method is believed to measure prothrombin specifically and accurately

With use of human plasma deficient in Ac globulin it has been shown that there is a correlation between Ac globulin concentration and apparent prothrombin concentration as determined by the original two stage technic It is thus possible to estimate Ac globulin content of human plasma by comparison of prothrombin titers obtained by the modified and the original two stage technics The modified prothrombin analysis gives the true prothrombin titer the original two stage procedure gives low prothrombin values which are proportional to the Ac globulin deficiency of the plasma

Prothrombin Consumption Test Its Clinical and Theoretical Implications are discussed by Armand J Quick and Jean E Favre Gilly[1] (Marquette Univ) The prothrombin consumption test is based on the principle that by determining prothrombin before and after coagulation is complete a measure of plasma thromboplastin that reacts with prothrombin is obtained In the original test blood was allowed to remain one hour at 37 C after coagulation before prothrombin of serum was determined Occasional inconsistencies in results were encountered and in searching for the cause of these it was found that when normal blood clots in a test tube all fibrinogen is converted to fibrin before a detectable diminution of prothrombin occurs This leads to the logical conclusion that the fibrin clot being uniformly dispersed through

(1) Blood 4 1281 1289 Dec mbe 1949

the mass of blood presents an enormous adsorbing surface which quickly and effectively removes nascent thrombin and thereby prevents sufficient accumulation to initiate the chain reaction that is mediated through the labilizing action of thrombin on platelets Almost all consumption of prothrombin therefore occurs only after serum has been separated from the clot either mechanically by centrifugation or spontaneously through clot retraction

As a result of the observation that prothrombin consumption is decidedly influenced by separation of serum from clot the original test was modified in order to control the adsorption factor of fibrin Instead of waiting one hour after coagulation before determining prothrombin of the serum eight test tubes each containing 2 cc blood were allowed to coagulate Every 15 minutes two tubes were centrifuged to one of which 0 1 cc of 0 4 M sodium citrate was added and prothrombin of the serum was determined at once and after three 15 minute intervals on each tube Since conversion of prothrombin is rapid immediately following the break in the intimate contact of the serum with the fibrin reticulum thrombin forms and accumulates during centrifugation therefore the prothrombin time done directly is abnormally short since it measures thrombin already present plus the amount formed during the test The latter increments can be prevented by adding sodium citrate to the clotted blood just before centrifugation so that thrombin formation is stopped and a true prothrombin value in serum is obtained

Prothrombin consumption varies considerably in normal persons In hemophilia and in thrombocytopenia it is very incomplete In hypoprothrombinemia the prothrombin may be very complete as in congenital hypoprothrombinemia of the component A deficiency type or surprisingly incomplete as in dicumarol® hypoprothrombinemia

The most remarkable finding is that in the test tube only a minute amount of prothrombin is converted to thrombin in coagulation of all the fibrinogen of the blood Only after separation of serum from the clot does prothrombin begin to decrease rapidly Obviously fibrin itself is the most important physiologic antithrombin Previously it was difficult to explain how this powerful latent clotting capacity of blood was held in check It is now clear that the strong adsorptive

property of fibrin not only guards against accumulation of thrombin but also prevents the autocatalytic reaction involving labilization of platelets by thrombin from being set in motion except at the site of vascular injury

Concentration of Component A in Blood, Its Assay and Relation to Labile Factor For clinical purposes it is advantageous to divide the clotting factors required for formation of thrombin into two categories thromboplastin formers and constituents of the prothrombin complex The latter are essential for prothrombin activity as measured by the one stage prothrombin time determination According to Quick agents in the prothrombin complex are labile factor components A and B and bound calcium The labile factor is characterized by its instability especially in decalcified plasma and its nonadsorbability by tricalcium phosphate Component A is the principle which is adsorbable by tricalcium phosphate requires vitamin K for its synthesis [is probably inactivated by sodium citrate —Ed] and is deficient in one type of congenital hypoprothrombinemia It is probably this component which is generally called prothrombin by other investigators Component B is difficult to define Its existence is postulated to explain a second type of congenital hypoprothrombinemia which is also hereditary and in which the labile factor and component A appear to be normal [Elsewhere Quick and Stefanini have presented evidence that prothrombin B is concerned with the conversion of prothrombin A from an inactive to an active form —Ed]

Desirability of having methods for quantitative estimation of the various constituents of the prothrombin complex is obvious Recently a procedure has been developed for estimating concentration of the labile factor and in the present report Armand J Quick and Mario Stefanini (Marquette Univ) describe experiments which not only yield a procedure for estimation of component A but also furnish results which show its relationship to the labile factor The one stage method for prothrombin time determination was used

When normal oxalated plasma was added in progressively increasing amounts to plasma from which component A of prothrombin was absent or very low owing to vitamin K deficiency removal by adsorption with tricalcium phosphate

( ) J Lab & Cl M d 34 973 982 J ly 1949

or congenital lack prothrombin time was characteristically decreased until approximately one volume was added to one volume of the defective plasma After this prothrombin time became the same as that of normal plasma This indicated that normal plasma supplies about twice as much component A as is required to attain a normal prothrombin time and that therefore component A is apparently not the specific determinant of prothrombin time even in the presence of an excess of labile factor Prothrombin time as determined by the one stage procedure therefore does not measure any particular constituent of the prothrombin complex but rather their composite effect

Amount of component A can be determined as follows By means of adsorbing oxalated plasma with tricalcium phosphate and treating the latter with sodium citrate an eluate is obtained which contains almost all of the component A present in plasma When this eluate is added in an amount equivalent to that in the volume of normal plasma from which it was obtained to plasma lacking component A normal prothrombin time is restored By adding progressively decreasing amounts of the eluate to component A free plasma a series of values of prothrombin time are obtained which correspond well with the original prothrombin curve Component A is active only if an adequate amount of labile factor is present

When this method for quantitative estimation of component A was used the concentration of component A in plasma of a patient with congenital hypoprothrombinemia was shown to be deficient Eluate obtained from his plasma when tested for component A potency either on normal calcium phosphate plasma or on his own plasma yielded the same low result whereas eluate from normal human plasma restored his prothrombin level to normal exactly as it did in normal calcium phosphate plasma

When severe hypoprothrombinemia was produced in chicks by means of a vitamin K free diet for 10 days an eluate of the plasma of these chicks showed no prothrombin potency when tested on hen tricalcium phosphate adsorbed plasma indicating a complete lack of component A It is logical to conclude therefore that deficiency of vitamin K produces a pure component A type of hypoprothrombinemia

Similarly in dogs hypoprothrombinemia resulting from dicumarol® could be promptly and completely corrected by addition of a concentrated solution of component A i e the eluate from tricalcium phosphate adsorbed plasma thus indicating that the basic defect in dicumarol® poisoning is also lack of component A

Parahemophilia (Owren) New Form of Hemorrhagic Diathesis E Frank N Bilhan and H Ekren[3] (Univ of Istanbul) describe a case

Man 29 had bled profusely on many occasions one epistaxis lasting 48 hours One brother had died of hemorrhage in infancy and the father was subject to abnormal bleeding In 1947 the patient had a sudden attack of hematuria unassociated with colic which continued intermittently for six months A second attack was accompanied by pain but no stone was found During the last attack in 1948 hematuria was accompanied by pain and x rays showed a kidney stone The urologist who advised nephrotomy requested a study of the patient s hemorrhagic diathesis to determine whether operation would be dangerous because of bleeding

Pseudohemophilia and true hemophilia were ruled out because there had never been petechiae ecchymoses or hemarthroses Blood platelets numbered 344 000 and bleeding time was six minutes Coagulation time was normal but the clot was not firm In repeated tests by Quick s method prothrombin time was 47 seconds When prothrombin time was 47 50 seconds the patient did not bleed but when it reached 60 80 he bled profusely The assumption that bleeding was caused by reduced prothrombin was untenable because vitamin K administered for 12 days had no effect Whole blood transfusions shortened prothrombin time immediately and for eight hours During an acute attack of hematuria with high fever prothrombin time reached 80 seconds but response to transfusion was immediately favorable and the operation performed without unusual bleeding

Tests were carried out to determine whether human or animal plasma free from prothrombin or a factor isolated from such plasma influences prothrombin time When the patient s plasma was diluted to one third its strength with salt solution prothrombin time was reduced to 45 seconds when calves plasma was used it reached a low of 40 seconds Prothrombin free normal plasma or its active principle according to Owren was obtained by precipitation with dilute acetic acid and dissolved after an hour in physiologic saline Either invariably reduced prothrombin time to 19 seconds The patient s plasma shortened the coagulation time of a true

(3) Acta haematol. 3 68 90 1950

hemophilic Owren s factor from the hemophiliac s plasma shortened the prothrombin time of the patient described

The authors state that this case and one reported by Owren are identical and they adopt the term parahemophilia proposed by Owren A plasma factor was absent in both cases which was not related to the thromboplastin but to the pro thrombin complex Three cases of idiopathic hypoprothrom binemia in the literature may belong in the category of para hemophilia It is recommended that future cases be studied from the viewpoint of the plasma factor

Hypoprothrombinemia Studies of Case of Idiopathic Type and Effect of Serum Administration are reported by Charles L Crockett Jr Donald Shotton Charles G Craddock Jr and Byrd S Leavell[4] (Univ of Virginia)

Girl 5 was hospitalized for study of abnormal bleeding which had occurred intermittently since age 2 weeks Episodes of severe epistaxis hematemesi and melena had occurred but there was no history of hemarthrosis Hematuria was present on admission No history of hemorrhagic phenomena in other members of the family could be elicited from the mother Prothrombin conversion time of *the mother s plasma was normal*

Examination revealed many old hematomas but no jaundice ad nopathy or hepatosplenomegaly Laboratory studies revealed 3 700 000 red cells 11 Gm hemoglobin 7 200 white cells normal blood and bone marrow differential counts 1 3 per cent reticu locytes hematocrit 39 sedimentation rate 6 mm in 1 hour 388 000 platelets bleeding time of 2½ minutes negative tourni quet test and normal clot retraction Prothrombin time ranged from 62 to 92 seconds and clotting time from 11 to 48 min utes Liver function studies were within normal limits Electro phoretic study of the blood revealed a normal protein pattern with no fibrinogen deficiency Direct examination of nail bed capillaries revealed normal appearance and normal response to traumatic rup ture Lack of response to large doses of synthetic vitamin K prepara tions seemed to exclude vitamin K deficiency Therefore it appeared that this patient had idiopathic hypoprothrombinemia Absence of any change in either subjective or objective clinical manifestations including signs of liver disease over three years of repeated observa tions substantiated this interpretation

Repeated mixture of normal plasma with the patient s plasma in equal amounts substantially lowered the prothrom bin time but not to normal levels Existence of a factor in normal blood which is necessary for rapid conversion of pro thrombin seems beyond dispute There seemed little doubt

(4) Blood 4 1298 1309 D mb 1949

that normal serum possessed a factor which was capable of accelerating prothrombin conversion in this patient's plasma. This factor or factors has been called Ac globulin. After the in vitro demonstration of a deficiency of Ac globulin in the patient's blood it was possible to bring about a decided reduction in the prothrombin time by intravenous administration of relatively small amounts (15-45 cc) of fresh normal (thrombin free) serum. A further reduction of prothrombin time to near normal values was brought about by combined whole blood and serum administration. Evidence suggested that partial correction of both prothrombin and Ac globulin deficiency resulted from such therapy.

These studies support the concept that serum contains an active substance which is capable of accelerating prothrombin conversion to thrombin. Deficiency of this substance may play a role in many types of hemorrhagic states. It is probable that alterations of Ac globulin are of particular importance in various types of prothrombin deficiency.

Coagulation Defect in Hemophilia with Particular Reference to Conversion of Prothrombin to Thrombin and Evolution of Prothrombin Conversion Accelerator. Most investigators agree that conversion of prothrombin to thrombin is retarded in coagulation of hemophilic blood. This is reflected in the high prothrombin activity of hemophilic serum. Clotting of hemophilic blood can be accelerated by addition of thromboplastin, normal plasma or fractions thereof. Recently substances have been described which, arising in blood during coagulation, accelerate conversion of prothrombin to thrombin in presence of thromboplastin plus calcium. Benjamin Alexander and Andre de Vries[5] (Boston) present data indicating that in the elaboration of one of these clotting factors, serum prothrombin conversion accelerator (SPCA), also the coagulation of hemophilic blood is abnormal.

Prothrombin activities of serums removed and oxalated one hour after coagulation from hemophilic blood were abnormally high. Conversely, SPCA activities were abnormally low. No correlation was evident between coagulation time and these serum entities.

In normal subjects accelerating coagulation by addition of thromboplastin increased SPCA and removed the last

(5) Blood 4 75 758 J n 1949

traces of serum prothrombin activity Restoring clotting time of hemophilic blood to normal in vitro by addition of small amounts of thromboplastin failed to lower residual serum prothrombin activity appreciably SPCA concentration was also unaffected When however larger amounts of thrombo plastin were supplied both prothrombin consumption and SPCA evolution were sometimes greatly increased attaining normal values It is striking however that in two subjects substantial amounts of serum prothrombin activity were still demonstrable although the parent blood had clotted in 180 seconds or less This is in marked contrast to what was ob served in normal subjects

Restoration of clotting time of hemophilic blood toward normal by in vitro or in vivo addition of normal plasma de creased residual serum prothrombin activity substantially in some ca es but activity rarely reached normal values SPCA however rose only slightly even when as much as 700 cc normal plasma was infused Addition of normal serum con taining substantial SPCA activity to hemophilic blood accel erated coagulation only slightly as compared with the clot promoting effect of the parent plasma

Hemophilic plasma and serums obtained one hour after coagulation were subjected to simultaneous prothrombin de termination by both one stage and two stage technics Whereas by the one stage procedure serum prothrombin ac tivity was no less than that of its parent plasma by the two stage method it was markedly less

Superiority of Vitamin K_1 Oxide over Menadione Sodium Bisulfite U S P and Synkayvite® in Reversing Dicumarol® Hypoprothrombinemia To establish a broader clinical basis for control of dicumarol® effect David F James Ivan L Ben nett Jr Peritz Scheinberg and John J Butler[6] (Atlanta Ga) administered menadione sodium bisulfite synkayvite® and vitamin K_1 oxide in large single doses to patients with hypo prothrombinemia induced by dicumarol® Efficiency of these substances was estimated on the basis of time elapsing be tween administration of the drug and conversion of pro nounced to moderate hypoprothrombinemia and time elapsing after administration of the agent until appearance of a pro thrombin level consistent with intravascular clotting

(6) A h I t M d 83 63 65 J 1949

Vitamin K_1 oxide was most effective in both respects For 26 patients given 0 5 Gm or more intravenously prothrombin time arrived and stayed at a level lower than that of 30 per cent normal plasma in an average of 15 hours When menadione sodium bisulfite (64 180 mg) was given intravenously to 19 patients this shortening of prothrombin time was achieved in an average of 4 7 days When synkayvite® (100 500 mg) was given intravenously to six patients an average of 5 3 days elapsed Six patients with severe hypoprothrombinemia treated with 0 1 Gm or more of vitamin K_1 oxide required an average of four hours to achieve a prothrombin concentration within what is generally regarded as a safe range In patients who have recently been given vitamin K_1 oxide the amount of dicumarol® needed again to prolong prothrombin time to beyond that of 20 per cent normal plasma is unchanged if menadione sodium bisulfite has recently been given but with vitamin K_1 oxide the amount of dicumarol® must be increased threefold

Analysis of the time required for achievement of dicumarol® effect in 101 patients showed that in about 1 of every 5 five or more days was necessary for a significant therapeutic effect with dicumarol® in the usual doses (*300 mg the first* day and 200 mg on each successive day) The authors data suggest that on the basis of the amount of dicumarol® needed by a given patient it is possible to predict how much may be necessary during a second course in the near future Five patients who were allowed to recover untreated from the effect of dicumarol® were treated a second time after at least two days during which prothrombin time was equal to that of normal plasma During the second course of dicumarol® requirements varied from the first course by no more than two doses Analysis of normal control values in a large number of determinations revealed their variability and the necessity therefore of using several controls if a proper dilution curve for prothrombin is to be derived

[This striking activity of vitamin K oxide confirms earlier observations by Davidson Aggeler and others According to Jacques vitamin K act by progressive displacement of dicumarol® from the liver For this reason perhaps the more slowly metabolized vitamin K oxide is more effective than other forms of vitamin K —Ed]

THE HEART *and* BLOOD VESSELS *and* THE KIDNEY

TINSLEY R. HARRISON M.D.

PART IV

THE HEART AND BLOOD VESSELS AND THE KIDNEY

PROGRESS IN THE CARDIOVASCULAR FIELD DURING THE LAST DECADE

The medical historian of the future will probably state that more progress occurred in the 1940 s than in any previous period of similar length He will consider as especially significant the better understanding that has developed of the psychologic impact of heart disease on the patient and the family and the realization that in a patient with complaints referable to the heart the physician s first duty is to alleviate fear regardless of whether or not the structural disease exists He would also deem especially important the fact that in this decade occurred the beginnings of a clear scientific rationale for more intelligent recommendation of rest versus activity and of the value and harm of the various postures These advances affect all types of heart disease and hence are particularly notable

Another basic principle which emerged during this decade followed the introduction by William Dock of the concept that senile deterioration of the myocardium occurs independently of coronary arteriosclerosis This involutionary change appears to be a least common denominator in almost all heart failure in patients over age 50 regardless of the apparent primary disease process The concept explains the frequency of heart failure in elderly persons with hypertension various valvular diseases thyrotoxicosis etc and the rarity of heart failure in younger persons (in the absence of active myocarditis) despite the presence of similar disorders

Instrumental Methods and Procedures

The usual history of new instruments is that of their initial use as research tools plus the gradually increasing clinical application as advantages and limitations become clarified The

striking advance in electrocardiography after the introduction of the precordial leads in the thirties was followed in the forties by the general introduction into clinical practice of the V leads and the unipolar limb leads The angiocardiographic procedure has demonstrated its usefulness in the diagnosis of congenital lesions It is not without risk and should be utilized only by those experienced with the method

The catheterization technic was perfected and its value as a research tool was demonstrated The greatest practical value of the procedure thus far has been in the differentiation of the various types of cyanotic congenital cardiac disease thereby improving the criteria for selection of patients suitable for the Blalock Taussig operation

Ballistocardiography a purely research method in the thirties emerged as a clinical procedure in the forties when its value in early diagnosis of coronary disease began to be apparent

To those interested in hemodynamics the most exciting development was the introduction of the electrokymograph Here at last was a tool which allowed the investigator to study the Starling curve in man Thus the basic physiology of the heart could be studied at the bedside The prediction may be ventured that the electrokymograph or some modification of it will eventually be the first tool to threaten the supremacy of the eye the hand and the ear in diagnosis of cardiac disease and the supremacy of the history in evaluation of the functional capacity of the myocardium

Diseases of the Heart

Congestive heart failure—During the early part of the decade the importance of disturbed renal function became apparent and it was at first thought that the demonstration of the importance of sodium retention by the kidney necessitated discarding the previously accepted ideas of Starling s concept of cardiac edema Toward the end of the decade it began to be recognized that the new advances while of great significance were additive rather than substitutive and that the concept of the 1930 s (and indeed of the previous century) that the basic mechanism of heart failure was elevation of pressure in the chambers of the heart was still valid Nevertheless the practical importance of the secondary renal factors and of the secondary increase in blood volume became evident

In the treatment of heart failure the outstanding advances

were the more rational use of digitalis following the develop ment of purified products the general recognition both of the value of sodium restriction and of its harm when carried to ex cess and practical and theoretical advances with regard to the mercurial diuretic Especially significant was the reduction of the hazard of pulmonary infarction through development of im proved methods of diagnosis and management of thrombo embolic disease

Congenital heart disease —The most dramatic developments were those in surgical treatment In the late thirties operative treatment of certain noncyanotic types of congenital heart dis ease was begun and during the forties it was demonstrated that both patent ductus arteriosus and coarctation of the aorta were curable These operative procedures when carried out by sur geons with proper experience are attended by comparatively low mortality Those patients with congenital disorders asso ciated with restriction of pulmonary blood flow and with right to left shunts were found to be strikingly benefited by the Blalock Taussig procedure Although complete cure cannot be achieved invalidism has been overcome and when considered in relation to the usually precarious preoperative state the mor tality rate has been gratifyingly low and is declining steadily

The development of successful surgical treatment was strong stimulus to improvement in diagnostic methods The consequent developments in the angiocardiographic and catheterization technics have been cited

The study of the relationship between maternal rubella dur ing pregnancy and the subsequent birth of a child with a con genital disorder of the heart opened for the first time the door to prevention

Rheumatic heart disease —The most important development in rheumatic heart disease occurred late in the decade when cortisone and ACTH began to be used The dramatic control of the disease with these compounds justified the hope for a truly successful therapy However long range follow up studies are needed before these new methods can be finally evaluated

The case for sulfonamide prophylaxis was just being estab lished when penicillin prophylaxis began to be advocated Pend ing long range investigations it would appear that the latter procedure will be the method of the future

Another notable step was the firm establishment of the hemo-

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(and other) arteries seems indisputable Less convincing but still intriguing is the idea that the normal values for blood cholesterol in the American population represent hypercholesteremia and that atheroma is less common in subjects with levels in the lower portion of the normal range The relative importance of intake synthesis excretion and destruction as determinants of the blood level remains in dispute The demonstration that cholesterol may be synthesized from 2 carbon fragments was of great importance and offers the first rational explanation for the increased tendency of obese subjects to develop atherosclerosis Since fat is oxidized by progressive splitting of 2 carbon fragments and since the Schoenheimer concept of dynamic equilibrium indicates that the fat depots are metabolically active rather than passive it is altogether probable that the total fraction of potential precursors of cholesterol available in the metabolic pool at a given moment is increased in obese subjects Thus the rationale for thinness as a means of preventing atherosclerosis appears to be established Less convincing is the concept of the specific importance of cholesterol restriction Pending further knowledge it would seem desirable to ascribe first importance to total caloric restriction second significance to restriction of fat (both mineral and vegetable) and third place to restriction of cholesterol per se

Strong evidence for the concept that the tendency to atheroma may be related not only to the quantity of fat but also to the quality—i e the state regarding dispersion and particle size—has recently been presented

Advances specifically outstanding in the management of coronary disease include those in the field of thromboembolism and the increasing evidence that nitroglycerin may perhaps have a curative (by widening collateral channels) as well as a symptomatic effect in persons with myocardial anoxia

The great practical gains resulting from the application of Frank N Wilson s basic principles to clinical electrocardiography are so well known as to require no further comment

Peripheral vascular disease —Here the advances were rapid Better means of recognizing peripheral thrombosis in its early stages were developed Anticoagulant therapy—a matter largely of theoretical interest in 1940—was made practical and its value was established by well controlled studies The importance of femoral ligation was demonstrated although the precise

lytic streptococcus as the most important (if perhaps not the sole) initiating agent The concept of the disturbed antigen antibody mechanism of the disease appears to rest on firm ground The importance of the various spreading factors involved in the hyaluronidase enzyme system would appear to have been demonstrated The relationship of the salicylates and allied substances to these factors has been shown and represents a promising avenue for further research

Bacterial endocarditis —Here is the most brilliant of all the practical advances The reduction in mortality from practically 100 per cent to less than 20 per cent in this fell disease as the result of antibiotic therapy requires no comment

Diseases of Blood Vessels

Hypertension —At the beginning of the decade an objective observer would probably have predicted that the rapid progress in knowledge of hypertension during the thirties would yield handsome returns in the forties This optimistic hope has not been justified The relative importance of renal pressor substances renal homeostatic mechanisms tending to prevent hypertension neurogenic and psychic factors endocrine disorders and unknown mechanisms remains obscure

The case for sodium restriction seems to be established for some patients but it is equally clear that this procedure has little or no value in most patients It seems that the beneficial effects sometimes obtained from the rice diet are chiefly but perhaps not entirely the result of the low sodium content of the diet The possible significance of the paucity of protein of cholesterol and of allergens in this diet is uncertain There is no evidence that rice as such has a positive value

The various types of surgical sympathectomy have been shown to be useful in delaying the progress of the disease in properly selected subjects It is as yet too early to predict whether or not the sympatholytic drugs will ever replace the operative procedures The results with veratrine compounds are of interest but their long range usefulness remains to be defined

Atherosclerosis —Although practical advances were limited theoretical knowledge increased at a rapid rate For the first time an attitude of optimism toward the future seems justified

The evidence that hypercholesteremia however induced favors the production of atheromatous changes in the coronary

to renal hypertension was not realized although advances were made the progress wa disappointing

To the philosopher (or in the present instance the pseudo philosopher) certain conclusions seem to emerge from this brief survey of the rapid progress made in the cardiovascular field during the past decade The first is that few problems in medicine are inherently insoluble If the problem of bacterial endocarditis can be largely solved if blue babies can live to be come pink adults if persons with congestive failure can be kept alive for many years and often for decades if an optimistic view point toward the probable future developments in atherosclerosis has emerged it would be folly to believe that disorders which now seem totally hopeless will remain so

The second conclusion is that the sharp lines between the ivory tower of research and the practical care of the patient are becoming blurred Fundamental advances in physics and chem istry are soon followed by better understanding of the mecha nisms of disease the result is the trial of new therapeutic pro cedures These procedures often require extensive clinical study by persons skilled in the scientific method before they can safely be utilized by physicians living at a distance from the best laboratories The public is on the one hand entitled to receive promptly the benefits of new discoveries without on the other hand suffering the risk of being victims of uncritical evaluation of untried remedies The medical profession is entitled to derive the satisfaction which comes from doing a first class job with its patients and from being in the forefront of intellectual advance Such satisfaction can be achieved only if physicians have free dom of action and independence of thought It is doubtful whether these conditions can be realized except through some plan which brings medical research and medical education closer to the profession To develop such a plan will require the exercise of wi dom and patience on the part of the profession the medical schools and the public

—TINSLEY R HARRISON

indications for this procedure rather than for anticoagulant therapy alone are still debated

The importance of surgical and chemical sympathetic block was demonstrated both for arterial and venous obstruction Whether the sympatholytic drugs will ever replace sympathec tomy is uncertain The drugs may be more valuable when a generalized effect is desired as in certain persons with hyper tension but surgical sympathectomy will probably remain the method of choice for the treatment of local vascular disorders unless an agent with long duration of action (weeks or months) can be developed for local injection

New technics for more precise study of local circulation were developed Those employing isotopes would seem to offer the greatest long range promise

Cerebral vascular disease —In this most neglected of all the important fields of medicine practical progress was almost nil The biochemists have begun to clarify a few of the mysteries concerning cerebral enzyme systems and a few individuals in the field of physical medicine continue to make valiant efforts Despite the paucity of practical advances the development of methods for studying cerebral blood flow and the metabolism of the intact human brain may be expected to lead to eventual therapeutic progress

Disorders of the Kidneys

The great advances were in the research field and resulted from the application of the technics and principles of Homer Smith to the study of disease It can be predicted that the infor mation so gained will be followed by important advances in treatment during the 1950 s

Other important advances included the growing evidence that acute glomerulonephritis is fundamentally a disorder of antigen antibody mechanisms the realization that renal con servation of solutes is equally as important as renal excretion of solutes in the fundamental homeostatic role of the kidneys the clear delineation of the concept of the fulminating nephroses (lower nephron nephrosis) and the gradual extension of knowl edge of the metabolic role of the kidneys

The old problem of the artificial kidney was attacked anew and may be approaching solution

As already indicated the expected rate of advance in regard

and frequently in lead II and inversion of T_3 and eventually T_2 Pulmonary diseases which cause cor pulmonale i e right ventricular strain depress the diaphragm and cause the heart to be vertically placed so that it is difficult to know whether changes in the ECG are due to right ventricular strain or to a vertical position of the heart Precordial leads are of some help in establishing diagnosis of right ventricular hyper trophy Whereas normally in V_2 R is very small and S is deep and in V_5 R is tall and S is small in right ventricular hypertrophy the reverse may be true

In children and in young adults widening and notching of the P waves are a reliable indication of auricular enlargement but in older persons such changes occur commonly and are not diagnostically significant Though QRS widening is fre quently encountered in association with long standing and ad vanced left ventricular enlargement it is due only in slight part directly to increased thickness of the myocardium

The simplest and one of the most useful measurements of heart size in x ray examination is the transverse diameter Assumption that the transverse diameter should be less than half the transverse diameter of the chest at the level of the diaphragm has been widely popularized but is crude and in exact More accurate standards based on weight and height have been established Diameters more than 10 per cent above the predicted value should be regarded as abnormal Two other diameters the long and broad are well known The long diameter extends from junction of the cardiac and vas cular silhouette on the upper part of the right border of the heart obliquely down to the apex on the left This diameter which is approximately 10 per cent greater than the transverse diameter is increased chiefly as a result of left ventricular enlargement The broad diameter is the greatest single diam eter from upper left to lower right heart border perpendicular to the long diameter These two diameters are of interest chiefly for their product the frontal cardiac area which is an expression of the two dimensional size of the cardiac shadow

Measurement of aortic caliber is difficult The left border of the descending aortic arch is visualized in frontal x rays and if the esophagus is filled with barium the ri ht border of the aorta is indicated by the aortic indentation of the

DIAGNOSIS

The articles in this chapter emphasize the importance of the simple clinical tools and particularly the information to be gained by physical examination of the heart In occasional instances electrocardiographic study is essential with regard to arrhythmias and in many instances this method is of great value in the interpretation of chest pain When the cardiac impulse cannot be felt radiographic examination may be invaluable in determining cardiac size In deciding what type of congenital heart disease is present elaborate special studies by angiocardiography and catheterization may be necessary But in most patients with cardiac disease the history and physical examination yield all the essential information and often this information cannot be obtained by any other means Thus in the final analysis diagnosis of acute pericarditis depends on the characteristic friction sounds whereas that of valvular disease depends on the interpretation of murmurs The patient s story remains the supreme court with regard to the functional integrity of the myocardium and of the coronary circulation The interest in special methods of examination should never replace the physician s desire to perfect himself in those older technics which remain the backbone of diagnosis —Ed

Cardiac Enlargement is discussed by Harry E Ungerleider[1] (Equitable Life Assurance Soc New York City) Hypertrophy and dilatation as a rule are closely associated but are detected by different diagnostic technics hypertrophy by electrocardiograms dilatation by x rays Changes may occur in shape if not in size of the heart which suggest hypertrophy such as rounding of the left ventricular contour in concentric left ventricular hypertrophy and elevation of the cardiac apex in right ventricular hypertrophy producing the *coeur en sabot* Enlargement seen in x rays means dilatation of cardiac chambers however

Left ventricular hypertrophy may be considered to exist when left axis deviation occurs in association with any of the following changes in the ECG amplitude of QRS (sum of R_1 and S_3) exceeding 2 5 millivolts or R wave in lead I over 15 mm depression of S T segment in lead I or lowering of T_1 below 1 mm Increased amplitude of QRS may be attributed to increased mass of left ventricular musculature S T segment and T wave changes are due to relative ischemia of the deeper layers of the left ventricle

Pattern of the ECG in right ventricular hypertrophy consists of right axis deviation plus S T depression in lead III

(1) Am. Pract. 1 286 98 M eb 1950

for a patient to have a complete cardiac work up with x rays and electrocardiograms when careful auscultation would have quickly revealed the nature of the disorder and might have resulted in a more accurate diagnosis because of observations overlooked or misinterpreted by other methods

Auscultation of the heart enables one to eliminate certain diagnoses e g if no murmurs whatever are heard even with the patient turned to the left lateral position or sitting upright subacute bacterial endocarditis or chronic rheumatic valvular heart disease can be eliminated fairly safely A more important contribution of auscultation is the establishment of a definite diagnosis by detecting certain abnormal sounds Pericardial friction almost invariably indicates acute pericarditis In most cases an apical rumbling murmur diastolic or presystolic in time is diagnostic of mitral stenosis With familiarity of the character of this murmur diagnosis is certain even if the murmur is faint or present only after effort or heard when the patient is lying on his left side This is also true of a faint early diastolic murmur at the base of the heart in the diagnosis of early aortic insufficiency It is not to be inferred that detection of cardiac murmurs always leads to a decisive diagnosis there are many instances especially when systolic murmurs are involved in which proper evaluation may be most difficult This does not detract from the value of auscultation but rather presents an additional challenge to analyze physical observations correctly

Another type of information derived from auscultation is what might be called clues to diagnosis The heart of a patient stricken with severe epigastric pain resembling acute pancreatitis or perforated peptic ulcer may show a classic diastolic gallop A snapping first sound while the heart rate is rapid and grossly irregular in the absence of any murmurs frequently indicates mitral stenosis in such a case

Apart from the evidence of valvular and pericardial disease which may be obtained by simple auscultation detection of arrhythmias or changes in quality of heart sounds is important Tripling of sounds (a gallop rhythm) is overlooked too frequently When the extra or third sound of a gallop can be identified as occurring in diastole it almost always indicates grave heart disease however it is not sufficiently appreciated that gallops in which the extra sound occurs during

esophagus therefore the diameter at this level can be ascertained by subtracting 2 mm representing the thickness of the esophageal wall This method is not dependable when the aorta is tortuous and the aortic knob projects to the left Where a portion of the aortic knob is indistinct true diameter of the aorta at this level may be ascertained by completing the circle, of which the aortic knob is an arc by means of a compass Diameter of the aorta at this level varies from 2 to 4 cm The table established for predicting transverse diameter of the heart from weight and height may be used equally well for the aortic arch diameter An aorta may be considered abnormal if the diameter exceeds the predicted value by 15 per cent

Configuration of the enlarged left ventricle varies somewhat depending on whether hypertrophy or dilatation predominates In hypertrophy as in early hypertension it becomes increasingly convex Enlargement of the left ventricle downward laterally and posteriorly is seen particularly in aortic insufficiency where dilatation of the left ventricular cavity predominates the diastolic volume necessarily being large because of increased systolic output Posterior enlargement of the left ventricle is best evaluated on fluoroscopy in the left anterior oblique position When enlargement is pronounced the left ventricular border which ordinarily clears the anterior border of the spine at an angle not greater than 60 degrees may not clear the spine at all

The right ventricle does not participate in forming the cardiac contour in the posteroanterior projection since it forms the anterior surface of the heart Nevertheless enlargement of this chamber may be indicated indirectly by its displacement of the right auricle to the right which causes increased prominence and convexity of the right border Even more characteristic is a straightening and increased prominence of the upper left heart border between the aortic arch and the left ventricular segment resulting from elevation and rotation of the pulmonary artery by the enlarged outflow tract or infundibular portion of the right ventricle The right ventricle is best studied in oblique views as is the left atrium

Diagnostic Value of Cardiac Auscultation is emphasized by Samuel A Levine[2] (Boston) It is not uncommon today

( ) J A M A 141 589 593 Oc 9 1949

mal as indicative of a so-called weak heart muscle Abnormalities in the first heart sound (like other auscultatory phenomena) will not be detected unless they are specifically listened for

These are but a few examples of auscultatory observations which can readily be made with a stethoscope

Variations in First Apical Sound Simulating So called "Presystolic Murmur of *Mitral* Stenosis' Phonocardiographic Study Mariano M Alimurung Maurice B Rappaport and Howard B Sprague[3] observed by means of phonocardiography that auscultatory presystolic *murmurs* may at times be an auscultatory *illusion* owing to certain variations in the first heart sound

A presystolic murmur at the apex is generally regarded as evidence of mitral stenosis It is commonly described as having a rapidly increasing intensity with a so called crescendo effect It is associated with auricular systole which increases velocity of blood flow through the stenosed mitral opening whereas the mid diastolic murmur generally begins with opening of the mitral valve Phonocardiography has shown that the crescendo character of the presystolic murmur is an inconstant phenomenon

The series studied consisted of eight patients all of whom were thought to have a presystolic apical murmur and yet phonocardiography failed to corroborate this auscultatory interpretation Instead certain variations of the first sound were noted which could explain the auscultatory error In most of the cases the murmur was clinically described as definitely crescendo The cases may be divided into three groups based on final clinical diagnoses The first group consisted of three patients who definitely had valvular disease Two had rheumatic heart disease with predominant aortic regurgitation and mitral regurgitation the other had syphilitic aortitis with aortic insufficiency In the two rheumatic cases the associated apical diastolic murmur with what was believed to be a presystolic crescendo led to the additional diagnosis of mitral stenosis Without a presystolic element the diastolic murmur itself would not have suggested mitral stenosis in view of the possibility of its being an Austin Flint murmur On the other hand in the third case a suspected Austin Flint mur

(3) New Engl J Med 241 631 636 Oct 1949

systole are often detected in persons who do not have heart disease

The confusion that prevails concerning the significance of loudness and character of the first heart sound is even more important Both heart sounds may be decreased in intensity if there is intervening tissue or space between the heart and the outside of the chest wall When the first heart sound is decreased and the second is not similarly affected its significance is entirely different The first heart sound is due mainly if not entirely to closure of the mitral and tricuspid valves however the abruptness or speed of ventricular systole affects the first heart sound When the contraction is hyperactive as in hyperthyroidism or anemia during effort or emotion or with certain fevers the first sound is often accentuated Valve leaflets close more abruptly and a brisk sound results There is a relationship also between the auriculoventricular interval (P R interval) and the loudness of the first sound The first sound is loudest when the P R interval is exceedingly short and generally faint when it is greater than normal From these observations it appears that when the mitral and tricuspid leaflets are wide apart or deep and low in the ventricular cavity the instant the ventricles contract the sound produced will be different (probably louder) than when they are nearer together or at a higher level If ventricles contract soon after the auricles the sound will be loud if there is delay between auricular and ventricular systole the valves will have had longer to float upward and nearly close and the first sound will be faint

Attention to intensity of the first sound as heard at the apex of the heart will often make it possible to estimate the P R interval s length and to recognize conditions in which there is a short P R interval others with a prolonged P R interval (first degree heart block) and those in which this interval is varying such as second and third degree heart block If the heart rate is regular first sound decidedly decreased and second sound normal it is fairly certain that the P R interval will be at least at the upper limit of normal or delayed systole Similarly if the rate is regular and slow and the first sound changes in intensity complete heart block with dissociation of auricles and ventricles is present It is an error to interpret a weak first sound when the second sound is nor

and the pressure therein increased Veins in the neck are of particular concern The prominent a wave in the jugular sphygmogram has been frequently referred to as has the presystolic impulse in the veins of the neck and in the liver The pronounced and chronic systolic pulsations of the deep jugular veins have also been emphasized

In a patient observed by Harry Vesell[4] (Beth Israel Hosp New York City) and found at autopsy to have tricuspid stenosis a pronounced presystolic impulse was felt over the right jugular vein just above the clavicle and over the sternocleidomastoid muscle This was of surprising force for a venous pulse It was easily timed by comparison with the systolic aortic impulse in the episternal notch palpated by the index finger of the other hand A see saw movement was conveyed to the two palpating fingers by the two vascular pulsations The strong presystolic venous impulse over the jugular vein was considered caused by the contraction of the hypertrophied right atrium this impulse was well transmitted to the neck because of the obstruction at the stenotic tricuspid orifice causing a damming back action the right atrium being unable to empty itself readily Transmission of the impulse was also aided by the increased venous distention and increased pressure in the large veins central to this area Vesell has never felt a presystolic impulse in the jugular vein in congestive heart failure without tricuspid stenosis This simple sign led to correct antemortem diagnosis in the patient observed

Xiphosternal Crunch Analysis of 106 Cases among 3 224 Army Separatees Xiphosternal crunch is a peculiar heart sound heard in the tricuspid area in normal persons Louis Schwab Gordon L Smiley and Werner P Meyn[5] emphasize the importance of recognizing the xiphosternal crunch as a common functional sound to be differentiated carefully from the sounds of pathologic significance heard in this area They found the incidence of xiphosternal crunch among 3 224 Army separatees to be 3 3 per cent Xiphosternal crunch was defined as a systolic sound of a crunching or spitting nature heard best at a point immediately to the left and above the xiphoid process in the absence of signs of organic heart disease In 58 per cent of the 106 cases in which this sound was heard

(4) Am J M d 7 497 500 O tobe 1949
(5) A I Med 31 8 234 A g st 1949

mur was not confirmed by subsequent phonocardiograms The second group comprised three patients with congenital cardio vascular anomalies coarctation of the aorta in one sub aortic stenosis in another and an undetermined anomaly as an element of Marfan s syndrome in the third In addition all were thought to have associated rheumatic mitral stenosis because of an apical diastolic murmur with the so called pre systolic crescendo In the third group of two patients mitral stenosis was diagnosed because of a presystolic murmur that was believed to be present No mid diastolic murmur was heard Phonocardiograms however disclosed no presystolic murmur Cardiac status in both cases was then declared nor mal Phonocardiograms were taken with the Sanborn Tri beam Phonocardiograph both the stethoscopic and the log arithmic microphones and the large open bell chest piece being used

The auditory illusion in these cases was due to several variant forms of the first heart sound in all of which the whole sound complex assumed a crescendo configuration The variations consisted in prolongation of the sound with its later elements of unusual intensity splitting of the sound so that the second element was more intense than the first and prolongation of the sound associated with an auricular gallop coming very close to the first sound In all variations however the first sound always started after the electrocardi ographic Q wave

Knowledge of such cardiac sound variations is important for they may produce an auditory illusion leading to serious diagnostic error in that the so called presystolic crescendo murmur at the apex is indicative of organic mitral stenosis The authors therefore emphasize caution in interpretation of this physical finding particularly in uncharacteristic cases in which the murmur may be rather short and faint and in which there is no other convincing evidence of mitral stenosis In such cases a careful phonocardiographic study is most help ful for correct clinical diagnosis

Tricuspid Stenosis Simple Diagnostic Sign It has re cently been shown that tricuspid stenosis is not rare and that the condition can often be diagnosed clinically Venous phe nomena are usually mentioned in descriptions of tricuspid valvular disease Veins of the body are engorged and dilated

14 1 per cent were moderately loud and only 0 5 per cent were very loud

In 137 of the 500 children 157 extra cardiac sounds were detected In 100 children a physiologic third cardiac sound was best heard at the apex or slightly to the right of this point in 34 a reduplication of the second cardiac sound was found best heard in the pulmonic area or along the left sternal border in 20 a reduplication of the first cardiac sound was best recognized at the apex and in 3 a midsystolic click was heard in the midprecordium

With few exceptions those murmurs best heard in the midprecordium possessed a characteristic vibratory or buzzing quality whereas those in the pulmonic area were basically blowing or humming Using these criteria as a guide in association with intensity pitch transmission etc identification of functional murmurs is greatly facilitated Apical location and transmission into the axilla is considered an important criterion for differentiating organic from functional murmurs However of the 182 midprecordial murmurs only 37 were audible at the apex Careful auscultation revealed that they were best heard to the right of the apex and that sounds at the apex represented diffusion of sounds which were of maximal intensity at another locus Thus if a murmur is audible at the apex or even to the left of it this is not a valid criterion for differentiating organic from functional murmurs A considerable degree of association existed between occurrence of the two types of adventitious sounds Neither however was found to be correlated with degree of anemia present in the patient or with age color sex state of nutrition or temperature

The authors concluded that the most valuable criteria for differentiating functional from organic heart murmurs in childhood are acoustic quality and point of maximal intensity Detection of innocent adventitious cardiac sounds in over one half of these children emphasizes the importance of careful cardiac auscultation

Aortic Sinus Aneurysms A Morgan Jones and F A Langley[7] (Univ of Manchester) report 2 cases of congenital and 2 of acquired aortic sinus aneurysms and compare them with 25 cases of congenital and 22 of acquired sinus aneu

(7) Brit. Heart J 11 325 341 Octobe 1949

quality of the sounds suggested crunching and in 39 per cent spitting

The sound may be caused by slight movements of the seventh costal cartilage under the cardiac thrust at its articulation with the sternum and xiphoid process Some degree of funnel chest occurred in 25 per cent of persons exhibiting the sound Possibly the abnormal sternochondral angle in this condition may favor production of the sound

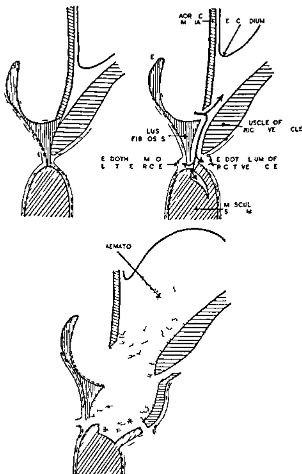
Occurrence of Innocent Adventitious Cardiac Sounds in Childhood was studied by Sidney Friedman William A Robie and T N Harris[6] (Univ of Pennsylvania) under conditions which closely simulated those in general office practice Criteria used for differentiation of functional from organic adventitious sounds were based on the results of cardiac auscultation Five hundred children aged 2 12 were given at least one special cardiac examination They were selected at *random from a medical outpatient department with no refer*ence to age, color sex or diagnosis except that those with a history or physical signs suggestive of rheumatic fever chorea congenital heart disease or hypertension were excluded Therefore all adventitious sounds noted were thought to be functional or physiologic in origin Each patient was examined in the erect and supine positions and again in recumbency following exercise consisting of 10 raise ups from the supine to the sitting position without assistance The point of maximal intensity transmission pitch intensity and quality of adventitious sounds were recorded Pulse rate was counted before exercise and before cardiac rhythm was noted

Of the 500 children examined 234 (46 8 per cent) had systolic murmurs over some area of the precordium All the murmurs were considered nonpathologic Of these 182 were of the greatest *intensity in the midprecordium i e in the* third fourth or fifth interspaces to the left of the sternum but definitely to the right of the apex In 91 children murmurs were loudest in the pulmonic area Thirty nine children had two separate murmurs each with its own point of maximal intensity and characteristic quality Ten children were found to have murmurs loudest at the apex and 1 loudest at the aortic area Thus in 234 children a total of 273 murmurs were detected Of the 273 murmurs 85 4 per cent were barely audible

(6) Ped at 4 782 789 Decembe 1949

rysms collected from the literature Acquired aneurysms may arise from any of the aortic sinuses Because of their large size they tend to extend upward often becoming extracardiac and rupturing outside the heart Cardioaortic fistulas were present in only six cases They encroach on intracardiac structures less often than congenital aneurysms Congenital cardiac defects were present in only two cases but acquired heart disease was invariably present usually syphilis or bacterial endocarditis *In one of the present cases there was a dissecting* aneurysm arising in the right coronary sinus at the junction of the aortic media with the annulus fibrosus (Figs 88 90) It is probable that the dissection arose as a result of active aortitis possibly rheumatic in origin

Congenital sinus aneurysms are confined to the right coronary sinus and the adjacent two thirds of the noncoronary sinus They are always small but because of their thin walls commonly rupture to form cardioaortic fistulas usually communicating between the right coronary sinus and the right ventricle or between the noncoronary sinus and the right atrium They remain entirely intracardiac and do not affect extracardiac structures nor rupture outside the heart They frequently cause disturbance of intracardiac structures especially the pulmonary valve which is often interfered with by right coronary sinus aneurysm and the tricuspid valve which may be encroached on by aneurysm arising from either sinus Congenital sinus aneurysms are nearly always associated with other developmental faults usually anomalies of the aortic cusps or bulbar ventricular septal defects Apart from bacterial endocarditis acquired heart disease occurred in only one case These aneurysms are believed to arise from defective development of the distal bulbar septum The patients are usually male In eight cases x ray studies disclosed no evidence of localized aneurysmal swelling Electrocardiographic findings were so inconstant that they gave little assistance *in* diagnosis The cause of death in 15 of 25 cases from the literature was heart failure which in 12 could be attributed to rupture in 2 to congenital cardioaortic fistulas and in 1 to rheumatic heart disease associated with an unruptured aneurysm Bacterial endocarditis led to death in six cases and intercurrent disease was the immediate cause of death in four Although it is difficult to diagnose an unruptured aortic sinus



F g 88 (top l ft) —N rm l tru t e of ao t c oot n t th o gh ght c on y D tr but n f la t t e s h wn by i te rupted l ne St ct s a named n F g e 89

F g 89 (t p r ght) —Mod of d se t on An l fib ha be n sepa ted from term nat n f ao t m d a S b q t d t of d ect n e d cated by arr ws

F g 90 (bott m) —A y m. By comparison w th F gu 89 th w y i wh h aneurysm ha form d n be een

(C tesy f Jo A M a d La gl y F \ B t H t J 11 3 5 341 Octob 1949)

arctation of the aorta in whom surgery had not been undertaken is presented by Bertrand G Wells Maurice B Rappaport and Howard B Sprague[9] (Boston) Coarctation was considered to be uncomplicated in all but one patient in whom the additional diagnosis of aortic regurgitation was made clinically Opinions differ as to which murmurs are characteristic in uncomplicated coarctation of the aorta and which are due to concomitant defects

A systolic murmur was present over the dorsal spine in all 15 patient and over the precordium in all but 1 A diastolic murmur was present in six patients over the dorsal spine and in five over the precordium Both systolic and diastolic murmurs were occasionally of greater intensity over the dorsal spine than over the precordium Such a distribution of intensity is never present in murmurs of isolated aortic valve deformity or patent ductus arteriosus and in none of the 15 patients were murmurs louder over collateral vessels than over the dorsal spine It is therefore probable that both systolic and diastolic murmurs are frequently present in uncomplicated coarctation of the aorta

Phonocardiographic tracings revealed the following facts Significant diastolic vibrations were present in tracings from the dorsal spine in every patient although in only six was a diastolic murmur heard Diastolic vibrations were characteristically of decrescendo configuration being a continuation from the systolic murmur Diastolic vibrations from the precordium were recorded in 10 patients although a diastolic murmur was heard in only 5 of these However the vibrations were usually of different configuration from those recorded from the dorsal spine and were therefore caused by a different mechanism in most instances the configuration of these vibrations resembled that in aortic insufficiency

The authors believe that systolic and diastolic vibrations from the dorsal spine are found on phonocardiography even more characteristically than they are heard on auscultation Reason that diastolic vibration may not be audible as a diastolic murmur are intensity of a loud systolic murmur may be such as to fatigue the human hearing mechanism which would mask the murmur in early diastole frequent absence of the second heart sound on auscultation over the back may

9 Am Heart J 38 69-79 July 1949

aneurysm it is one of the silent congenital lesions to be suspected when bacterial endocarditis develops in a heart apparently previously healthy

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CONGENITAL HEART DISEASE

The recognition of the various types of congenital anomaly of the heart is no longer a matter of academic interest but involves the practical decision of operability The articles presented here are valuable in this respect In view of the increasing interest in the surgical treatment of the cyanotic types of congenital cardiac disease it is important to realize that arteriovenous communications in the lung may produce a clinical state characterized by cyanosis polycythemia and clubbing of fingers Diagnosis and treatment of this condition are considered in the last abstract of this chapter —Ed

Circulation Times in Congenital Heart Disease K D Allanby[8] (Guy s Hosp London) reports results of estimating arm tongue and arm lung times in 36 patients suspected of having congenital heart disease Agents used were 20 per cent sodium dehydrocholate and 50 per cent saccharin for arm tongue time and 5 per cent paraldehyde for arm lung time There were no fatalities and no evidence of venous thrombosis or other complication except that about half the subjects complained of pain in the arm after paraldehyde and two became nauseated after decholin®

Results showed that measurement of arm tongue and arm lung times together is a reliable simple and safe method to be used for diagnosis of a right to left shunt It is most important that both times be estimated together as the only satisfactory evidence of a shunt is that they agree within two seconds of each other This alone can indicate that substances introduced into the right side of the heart reach a point on the great and lesser circuits simultaneously and there must be a communication between the two before the lung capillaries are reached Further the blood must be passing from right to left Failure was encountered in only three cases and in these it was attributed to use of too little saccharin Five patients had normal arm tongue times in each the arm lung time equaled this demonstrating the possibility of error if arm tongue time is taken alone as a guide to the presence or absence of a shunt

Sounds and Murmurs in Coarctation of Aorta Study by Auscultation and Phonocardiography on 15 patients with co

(8) B r H t J 11 165 169 Ap l 1949

shadow made by the ascending aorta and evidence of anterior displacement of esophagus and trachea in the left anterior oblique view Since surgery apparently gives permanent relief from symptoms clinical diagnosis of a double aortic arch is important

Analysis of 49 cases proved at autopsy or operation to have a double aortic arch with or without obliteration of part of the left arch revealed a striking correlation between occurrence of severe symptoms and duration of life All but 2 of the 19 infants had symptoms referable to the double aortic arch Fourteen of the 17 infants with symptoms died as a direct result of the malformation surgery was successful in 3 of 5 infants The high mortality in infants was in striking contrast to that in older patients of 23 patients over age 2 all but 6 lived to be 39 or older and only 3 had symptoms referable to the double aortic arch This analysis indicates that if a double aortic arch causes symptoms of constriction the symptoms will develop during the first two years of life Surgery is indicated only in patients who have such symptoms It cannot be stressed too strongly that incidental finding of a double aortic arch is not an indication for surgical division of the arch Operative mortality is high two of seven patients who underwent surgery died

A double aortic arch in which both components are patent throughout is more likely to produce symptoms than a double aortic arch in which one component is partially obliterated The process of obliteration does not appear to cause symptoms If obliteration occurs only the left component has been involved in all cases reported It is unusual for a double aortic arch to be associated with malformation of the heart though its association with other vascular abnormalities is less rare

Congenital Aortic Septal Defect A defect in the wall of the ascending aorta leading to free communication with the adjacent pulmonary artery is a rare congenital abnormality The opening in the anterior wall of the aorta is just above the semilunar cusps and leads directly into the pulmonary artery J H Dadds and Clifford Holye (London) report an example of this anomaly of value chiefly because there were no other congenital defects

Boy 14 was hospitalized for increasing dyspnea on exertion and

(2) Brit. Heart J 11 390 397 October 1949

obscure the fact that the murmur extends into early diastole

Synchronous records of radial and femoral pulses can be recorded satisfactorily and the authors believe that demonstration of abnormal asynchronism constitutes a valuable test in diagnosis of coarctation of the aorta and should be more widely used

Double Aortic Arch Report of Two Cases and Review of Literature is presented by Herbert E Griswold Jr and Maurice D Young[1] (Johns Hopkins Univ) A double aortic arch results from persistence of both fourth branchial arterial arches the arches fuse with the dorsal aortas to form the descending aorta resulting in a vascular ring Usually a large right aortic arch passes to the right of the esophagus and trachea *in a posterior direction turns to the left passing* behind the esophagus and trachea and connects with a small left aortic arch The small left aortic arch passes laterally to the left in front of the trachea and then turns posteriorly to join the right aortic arch which continues downward as the *left descending aorta Usually the right common carotid* artery and then the right subclavian artery arise independently from the right aortic arch the left common carotid artery and the left subclavian artery arise from the left aortic arch

The clinical picture of stridor and dysphagia may be present *during the first few months of life because of constriction* of the esophagus and trachea by the double aortic arch Criteria for diagnosis of a double aortic arch include susceptibility to bronchopneumonia stridulous breathing chronic cough head retraction malnutrition and increased respiratory distress *during feeding Clinical signs are dulness to the right of* the sternum visible systolic pulsation in the right supraclavicular fossa displacement of trachea to the left tracheal tug obstruction to free passage of a stomach tube at the level of the third dorsal vertebra with pulsation transmitted along the tube and maximal *intensity of the aortic second sound in the* region of the head of the right clavicle

Roentgenographic criteria include shadow of the aortic knob lying to the right and displacing the esophagus and trachea to the left *in the anteroposterior position the aorta lying behind the trachea and esophagus and displacing them* anteriorly in the right anterior oblique position a wide

(1) Pediatrics 4 751 768 December 1949

shadow made by the ascending aorta and evidence of anterior displacement of esophagus and trachea in the left anterior oblique view Since surgery apparently gives permanent relief from symptoms clinical diagnosis of a double aortic arch is important

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for palpitation He had had difficulty in breathing since infancy and activities had been severely curtailed He was a pale stunted youth with a kyphotic chest the anterior wall of which bulged forward prominently on the left side Cardiac pulsation was diffuse and thrusting with the impulse maximal in the seventh space 16 cm left of the midline The beat was regular A diastolic thrill was palpable just inside the cardiac impulse and also left of the sternum at the base Systolic and diastolic murmurs were heard all over the pre cordia the latter louder in the pulmonary area and just internal to the impulse The systolic element loudest in the aortic area was well conducted to the root of the neck Both heart sounds were audi ble in all areas and the pulmonary second sound was accentuated Blood pressure was 130/40 and pulse collapsing Neither cyanosis nor clubbing were present nor had he any congestive failure

Radioscopy showed a huge aneurysmal shadow comprising the pulmonary artery and aorta astride the greatly enlarged heart The aortic component was normally located but very pulsatile No sep arate aortic knuckle could be seen In oblique views the ascending aorta was prominent and a barium swallow showed a combined aortopulmonary impression Both ventricles were large the right larger than the left There was a pronounced hilar dance

In the next few months the patient had recurrent fainting spells and increasing loss of breath and died in congestive heart failure one year after study At autopsy the heart greatly enlarged was found to be surmounted by a large aneurysmal sac comprising the main pulmonary artery and the contiguous aorta Both ventricles were hypertrophied and dilated particularly the right one Auricles were not enlarged Septa were normal The aneurysmal sac showed a wide communication between the hugely dilated pulmonary artery and the base of the aorta just above the valves The defect measured 6×5 cm The aorta itself was hypoplastic Other organs were normal aside from congestion

Though survival is variable in congenital aortic septal de fects the physical limitations the defects impose appear to be almost uniform Symptoms of cardiac insufficiency from early infancy are always recorded Most patients died in congestive heart failure Cardiac murmurs reported in 11 cases vary greatly Basically the signs are similar to those of any other free leakage from the aorta above the cusps as with a patent ductus The heart is always enlarged especially the right side Site of the defect is remarkably constant and the lower border is formed by a smooth ridge of tissue separating the aortic and pulmonary sinuses The defect is usually small and the fine smooth edges are characteristic and distinguish the con genital from the commoner acquired communication between aorta and pulmonary artery Other congenital cardiovascular

defects are usually absent Clinical diagnosis of congenital patency of the aortic septum is difficult In none of the recorded cases was diagnosis made in life In this case the authors believed they were dealing with a complicated defect including a patent ductus arteriosus and probably an atrial septal defect Diagnosis depends primarily on signs of a free leak from the aorta in the presence of a dilated pulmonary arterial tree and enlargement of both ventricles Such a combination is rare enough if patent ductus either alone or with an atrial septal defect is excepted When patent ductus is the sole abnormality enlargement of the heart and of the pulmonary artery and its branches is rarely as striking as that found with large aortic septal defects If the aortic septal defect is small the difference from a patent ductus is less obvious Perhaps in the future retrograde angiocardiography may resolve the difficulty It is said to outline a patent ductus clearly and would almost certainly show the site and size of an aortic septal defect

Congenital Tricuspid Atresia Classification by Jesse E Edwards and Howard B Burchell[3] is based on study of 42 cases reported in the literature and 3 cases observed personally The circulatory defect in congenital tricuspid atresia may be described simply as a functional two chambered heart Common to all cases are atresia of the tricuspid orifice patency of the atrial septum and a large mitral orifice leading into a large ventricular chamber Atresia of the tricuspid orifice is represented by the absence of a right atrioventricular orifice Patency of the atrial septum is in most cases represented by a retention of the fetal type foramen ovale

Relation of the great vessels to each other and to the ventricular part of the heart varies among cases of tricuspid atresia The varieties of interarterial and arterioventricular relations constitute four groups which form the basis for the anatomic classification of congenital tricuspid atresia presented (1) no transposition of the great vessels and (*a*) pulmonary atresia closed ventricular septum or (*b*) subpulmonary stenosis (2) transposition of the great vessels and (*a*) pulmonary or subpulmonary stenosis or (*b*) no pulmonary or subpulmonary stenosis

In type 1*a* the left ventricle has a large capacity and its

(3) M Cl N rth Am 33 1177 1196 J l 1949

wall is thick The ventricular septum is completely formed The right ventricle is minute lies virtually hidden in the right upper wall of the large left ventricle and plays no role in circulation It is merely an isolated endocardial lined chamber since both the tricuspid and the pulmonary valve orifices are atretic The pulmonary atresia usually occurs at valve level the pulmonary trunk above valve level being hypoplastic but patent Death during infancy is the rule in patients with this type of tricuspid atresia

Type 1b is the most common of tricuspid atresias The great vessels are correctly interrelated The pulmonary trunk is somewhat narrower than normal but usually of adequate caliber to be able to carry a sufficient amount of blood to the lungs were there no subpulmonary stenosis A large ventricular chamber into which blood flows through the mitral orifice freely communicates with the aorta and communicates by means of a narrow tract with a smaller narrow ventricular chamber The upper extremity of the small ventricular chamber communicates with the pulmonary orifice The tract connecting the two ventricular chambers is narrow and constitutes the major barrier to blood flow from the larger ventricular chamber to the lungs Mean age at death of 22 patients with this type of tricuspid atresia was 7 months

As in all types of tricuspid atresia type 2a displays a large mitral orifice which leads into a large ventricular chamber Transposition of the great vessels is present There is also a diminutive ventricular chamber lying along the right side of the larger chamber which appears as a diverticulum While stenosis may exist at valve level and in the pulmonary trunk it is usually subpulmonic

In type 2b the malformation is identical with type 2a in all respects except for the state of the pulmonary circulation In type 2b the pulmonary trunk arises posterior to the aorta as in type 2a but there is no pulmonary or subpulmonary stenosis Judging from the reports on tricuspid atresia it is apparent that among patients with transposition of the great vessels those with subpulmonary or pulmonary stenosis have a much better chance of survival than those in whom no barrier to pulmonary blood flow exists

It has been suggested that transposition of the great vessels would favor longevity in cases of tricuspid atresia How

ever presence or absence of transposition per se will not determine degree of anatomic obstruction to pulmonary flow Survival to adulthood seems determined in part by chance but probably also by a balanced systemic and pulmonary blood flow In tricuspid atresia of type *2b* and perhaps in type *1a* wherein there is no barrier to pulmonary flow it is doubtful that benefit would be derived from an anastomotic operation such as the Blalock Taussig There is in contrast to the situation in the other two types of tricuspid atresia in which there is a barrier to pulmonary flow and in which an anastomotic operation is of benefit

Occurrence of Chronic Cyanosis in Cases of Atrial Septal Defect Atrial septal defect has been classified as a late cyanotic lesion one associated with cyanose tardive terminal cyanosis due to a reversal of the direction of the intracardiac shunt which occurs with cardiac failure increasing pressure in the right auricle It has also been stated that in atrial septal defect there is never the intense cyanosis and concomitant clubbing which are so characteristic of a venous arterial shunt Arthur Selzer and Alvin E Lewis[4] (Stanford Univ) observed a patient 35 with chronic cyanosis polycythemia and clubbing of digits who at autopsy was found to have an uncomplicated atrial septal defect They therefore reviewed autopsy reports in cases of atrial septal defect collected from the literature in which chronic cyanosis was observed

Of 180 cases of proved atrial septal defect with or without concomitant mitral stenosis 11 were thought to represent atrial septal defects with chronic cyanosis Cyanosis had been present since birth in two patients and in most of the others it appeared in the second decade Cyanosis was described in most cases as moderate in some as severe Clubbing was present in all except one Polycythemia was reported in seven Histologic findings in these cases did not differ from those in other noncyanotic cases Large defects involving most of the atrial septum were common among cyanotic patients but there was no apparent relation between size of the defect and presence of cyanosis Complicating mitral stenosis apparently rheumatic in origin was recorded in three cases

It is thus apparent that cyanosis not related to cardiac fail

(4) Am J M S 218 516 524 N mb 1949

ure may occur in cases of atrial septal defect with or without complicating mitral stenosis Degree of cyanosis and of accompanying polycythemia and clubbing and age of their onset places some of these cases definitely in the cyanotic group of congenital heart disease though they constitute only a small fraction of the total number That atrial septal defect may take the form of morbus caeruleus introduces a new problem in differential diagnosis of congenital heart disease With cyanosis moderate in degree and appearing in late childhood differential diagnosis between the Eisenmenger complex and atrial septal defects may be impossible by ordinary means and may have to rest entirely on results of venous catheterization of the heart

In addition to the diagnostic difficulty this problem raises the question whether cyanosis associated with atrial septal defect is due to the congenital defect itself or to complicating and secondary factors With the clinical and pathologic evidence pointing to a large volume of blood being shunted from the left to the right auricle the most likely cause of cyanosis appears to be a free mixing of blood in large septal defects and/or anatomic conditions permitting a stream of venous blood from the great veins to enter the left auricle directly

Arteriovenous Aneurysm of Lung To stress the importance of earlier recognition of a treatable condition Charles Baker and J R Trounce[5] (Guy s Hosp London) report two cases and review present knowledge of this disease Case 1 follows

Man 27 was referred for supposed cyanotic congenital heart disease to see if he was suitable for a Blalock Taussig operation Cyanosis which was gradually and steadily progressive was noticed at age 4 and a year later a diagnosis of congenital heart disease was made

Examination revealed a spare well built man with gross cyanosis and marked clubbing of fingers and toes He was breathless on slight exertion but there was no orthopnea Neck veins were not distended liver was just palpable but not tender Lung bases did not sound wet but there was slight pitting edema of the ankles. Pulse was regular Heart showed no clinical enlargement and no murmur Pulsation in the second left intercostal space was the only finding of note Screening showed a heart slightly enlarged (13/25 cm) with the pulmonary conus prominent and an enlarged right ventricle In the

(5) Brit Heart J 11 109 118 Ap 1 1949

right lower lung field there was a circumscribed shadow with a well defined margin calcified in its lower part This was connected to the right hilus by a vascular shadow and there was pulsation from hilus to tumor An electrocardiogram showed marked right axis deviation with broad and prominent P waves in leads I and II and an inverted T in lead III

After the shadow in the lung had been seen the two important points needed to clinch the diagnosi of arteriovenous aneurysm *were looked for and found On listening at the right base posteriorly* there was a well marked localized systolic murmur but no diastolic element Angiomas were found on the inner side of the lips and on the buttocks and it was clear that a seborrheic disfigurement and the deep cyanosis had masked small angiomas on the face Blood picture showed severe polycythemia

Diagnosis of arteriovenous aneurysm of the lung was made and operation performed During operation the right middle lobe bron chus was wounded and it was necessary to remo e both the right lower and middle lobes This was difficult because of multiple va cular adhesions to the chest wall and diaphragm and there was con siderable blood loss Although cyanosis disappeared the patient s condition remained poor after surgery X ray revealed complete collapse of the right upper lobe and de pite bronchoscopy he died some 30 hours after operation

Examination of the surgical specimen revealed that the pulmonary vein leaving the lower lobe was grossly dilated and communi cated with a large thin walled loculated system of spaces Cut sur face of the lower lobe showed a multilocular hemangioma A branch of the pulmonary artery communicated directly with this cavernous space without capillary intervention Sections showed typical cavernous hemangioma

Cyanosis from childhood or early adult life with clubbing and polycythemia are the most important features of arterio venous aneurysm of the lung Physical signs in the heart are uncommon but a murmur may be heard in the chest corre *sponding to the invariable finding of an opacity in lung* x rays Associated vascular lesions in skin mucous mem branes and lips are common Cyanosis is slowly progressive and is followed by dyspnea restricted activity and eventually incapacity Hazards to life are from anoxemia polycythemia and hemorrhage from the aneurysm rather than from heart failure The commonest misdiagnosis in early life is congeni tal heart disease but the condition may also be mistaken for polycythemia rubra vera if cyanosis first develops in adult life or pulmonary tuberculosis when hemoptysis occurs with the undiagnosed x ray opacity

Arteriovenous aneurysm *of the lung is successfully treated*

by removal of the aneurysm by lobectomy or by pneumonectomy Surgery is a reasonable risk and indicated in patients with lesions large enough to cause cyanosis

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RHEUMATIC HEART DISEASE AND BACTERIAL ENDOCARDITIS

Induction of Cardiac Lesions, Closely Resembling Those of Rheumatic Fever, in Rabbits Following Repeated Skin Infections with Group A Streptococci Experiments have shown that focal infections of rabbits with Streptococcus viridans group A or C resulted in development of clearcut cutaneous and general hyperreactivity to the homologous infecting strain which was enhanced by frequent minute intracutaneous inoculations These observations led George E Murphy and Homer F Swift[6] (Rockefeller Inst) to become interested in the similarity of these phenomena to rheumatic fever in human beings and to investigate whether such animals had cardiac lesions resembling those of rheumatic heart disease Because of the difficulty of repeatedly infecting rabbits' throats and sinuses it was decided to inoculate the skin every month or twice a month with group A streptococci of different serologic types different types having been found to produce greater hypersensitivity than repeated infections with one type of organism

Animals were given 2 10 injections of streptococci of different serologic types during 3 20 months An elevated erythrocyte sedimentation rate leukocytosis anorexia weight loss postexertional dyspnea occasional transient pulmonary rales tachycardia and irregularity of cardiac rhythm developed in many of them

Microscopic examinations of the hearts of rabbits which died of infection or were killed while ill revealed focal alterations in connective tissue framework in blood vessel adventitia valves endocardium epicardium and myocardium Collagenous fibers were swollen eosinophilic and sometimes poorly stained Among such cells were found nodular collections of large irregularly shaped cells of unusual staining

(6) J Exper Med 89 687 698 June 1949

properties in most instances these granulomas were asso ciated with capillaries Interstitial valvulitis most marked in the middle of the cusp were observed on mitral and aortic valve leaflets and also on the right auriculoventricular valve The coronary arterial system was likewise involved and microscopic changes resembling those seen in patients with rheumatic fever were observed Neither bacteria nor any structures resembling inclusion bodies were seen

Since the cardiac lesions found in these animals were not found in control animals it was concluded they were due to successive cutaneous infections with group A streptococci of different types The striking histopathologic resemblance of these lesions to human rheumatic fever is of great interest

Subacute Bacterial Endocarditis Diagnosis and Present Day Treatment In the experience of Leo Loewe[7] (Long Island College of Medicine) positive blood cultures can be obtained in 85 95 per cent of patients with subacute bacterial endo carditis In the absence of positive blood cultures clinical diagnosis is generally accepted in patients with rheumatic or congenital heart disease an insidious illness with weakness and low grade fever and cutaneous or visceral embolization and splenomegaly When diagnosis rests between subacute bacterial endocarditis and rheumatic fever trial administra tion of penicillin should be made

In approximately 90 per cent of cases the infecting agent is streptococcus of the viridans or nonhemolytic type Cultures on suitable mediums must be seeded at the bedside and in cubated promptly Pour plates should be made as they often facilitate interpretation of questionable broth cultures Inocu lum of blood must be adequate If the patient is under peni cillin treatment cultures should contain penicillinase to coun teract penicillin All blood cultures should be incubated for three weeks before they are declared negative

In vitro sensitivity of the organism must be determined in every case Organisms inhibited by less than 0 1-0 5 units of penicillin/ml of test broth are considered sensitive to daily dosages of 2 000 000 units of penicillin Patients with organ isms requiring 10 30 units/ml or even more of test broth may be given prodigious daily dosages (10-40 million units) of penicillin with or without enhancing agents such as sodium

(7) Am P ct 1 349 361 Ap 1 1950

para aminohippurate or preferably, carinamide Carinamide 3-4 Gm every four hours is given orally day and night except in patients with impairment of renal function No serious side effects have been encountered

Intensive penicillin therapy is continued for four to five weeks If relapse takes place and this is usually evident within two weeks larger doses must be given and continued for a longer time at least eight weeks Continued positive blood cultures for more than a few days after starting treatment are considered unequivocal evidence of inadequate dosage In Loewe s series of 124 unselected consecutive patients with subacute bacterial endocarditis due to known organisms recovery took place in 104 Total penicillin dosage ranged from 1 400 000 to 927 000 000 Oxford units If despite acceptable penicillin blood levels the clinical picture suggests that infection is not being satisfactorily controlled streptomycin aureomycin or chloramphenicol may be given in addition If blood cultures are negative treatment must be determined clinically

To prevent subacute bacterial endocarditis foci of infection should be eradicated and antibiotics used when respiratory dental or other infections occur in patients with valvular heart disease In addition because there is a tendency to recurrence patients who have recovered from subacute bacterial endocarditis may be vaccinated Loewe vaccinated 50 recovered patients with a polyvalent vaccine composed of five strains isolated from the blood stream of patients during the active phases of the disease Results to date have been encouraging

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HYPERTENSION

In examining a patient with hypertension the physician should seek first for those causes which are curable such as tumor of the adrenal medulla or coarctation of the aorta Most patients with hypertension fall into the "essential" group the etiology of which remains uncertain In properly selected cases sympathectomy has a beneficial effect but is rarely curative The same may be said for psychotherapy Drastic restriction of sodium in the diet is beneficial in many younger patients but is usually ineffective in the older group Recent experimental studies indicate that there may be other dietary factors such as the intake of protein or of total calories Reports on the veratrum alkaloids are encouraging particularly those regarding protoveratrine Further investigation of these compounds is merited —Ed

Certain Pressor Depressor Tests in Essential Hypertension Comparison and Comment A number of procedures have been used to test maximal and minimal variations in patients with high blood pressure The cold test breathholding test posture test and response to mental stress are pressor tests Sodium amytal® or pentothal[8] sedative tests spinal block intravenous administration of tetraethylammonium and hyperventilation with carotid sinus pressure are some of the depressor tests

To determine how well these procedures reveal the range of variation and the maximal and minimal levels which occur spontaneously Teodoro Fostelli (School of Medicine Bologna Italy) and Robert Sterling Palmer[8] (Massachusetts Gen l Hosp) compared certain of these tests with observed spontaneous variations in 123 unselected patients with hypertension A combined posture and cold test the breathholding hyperventilation carotid sinus pressure test sodium amytal® sedative and mental stress tests were studied

Results of these procedures were simply to emphasize what is already known namely that blood pressure in essential hypertension is variable In the authors opinion variability of blood pressure as revealed by these tests does not classify hypertension into different grades and the variabilities are doubtful guides to prognosis and selection of patients for medical or surgical treatment Of these so called tests the simplest and least time consuming is the breathholding hyperventilation carotid sinus pressure test The mental stress test is useful in demonstrating the pressor factor to the patient and thereby encouraging acceptance of psychotherapy

In contrast to these maneuvers which demonstrate vascular hyperreactivity in essential hypertension there remain two tests worthy of the name because they are seemingly specific The first is the histamine test for pheochromocytoma of the adrenal gland It is dangerous but may be indicated when blood pressure is normal—though not if the history includes characteristic attacks of the pheochromocytoma syndrome and not if a typical attack occurs under observation The second test safer because it is a depressor test is use of benzodioxane It seemingly is specific for pheochromocytoma when blood pressure is elevated between attacks The physi

(8) Am. P ct 4 9 13 S ptembe 1949

cian should be alert to this possibility and the test should be used even though many negative results may be anticipated

Follow up Study of 243 Cases of Eclampsia for Average of 12 Years is presented by Charles I Bryans Jr, and Richard Torpin[9] (Univ of Georgia) Subsequent pregnancies (565) occurred in 188 women Of these 22 9 per cent resulted in either stillbirth or abortion (almost twice that expected in general) At least 203 pregnancies (36 1 per cent) were complicated by toxemia and 56 4 per cent of the 188 women had at least one toxemic pregnancy (four to six times the general rate of occurrence) Eclampsia recurred 27 times One woman had two subsequent attacks Incidence of repeated eclampsia was 4 8 per cent (7 32 times greater than the usual rate reported by various authorities) Previous to the original attack of eclampsia there had been 267 pregnancies in 82 women Of these 7 7 per cent were toxemic—approximately the usual incidence of toxemia

During the follow up period 27 women died 4 of eclampsia 5 of some manifestation of cardiovascular disease 4 of chronic glomerulonephritis and the others of unrelated causes Blood pressure of 47 women (21 4 per cent) was 140 or more systolic or 90 or more diastolic Incidence of hypertension in white women was 17 7 per cent and in Negroes 26 per cent Mean age of the white women was 43 7 years and of the Negroes 35 2 years For women of this age group incidence of hypertension was not significantly high However among the younger women hypertension was found more often than would be generally expected Elevated blood pressure was present in 8 9 per cent of women aged 20 29 Incidence of abortion or stillbirth and of toxemia was lower in the subsequent pregnancies of the hypertensive women than in those with normal blood pressure This was also true in the pregnancies preceding the original attack of eclampsia

The authors conclude that eclampsia is a specific disease of pregnant women and not a manifestation of chronic nephritis or of hypertensive cardiovascular disease, although either of these conditions may precede the attack of eclampsia and possibly make the patient more susceptible to toxemia Neither does eclampsia or nonconvulsive toxemia cause chronic nephritis or hypertensive cardiovascular disease Pa

(9) Am J Ob t & Gynec 58 1054 1065 December 1949

tients who have once had eclampsia or pre eclampsia are more likely to have subsequent toxemia and a high incidence of stillbirths and abortions because the same etiologic factors environment diet etc are likely to remain more or less constant and to provoke the same results in subsequent pregnancies

Prognosis in Arterial Hypertension Comparison between 251 Patients after Sympathectomy and Selected Series of 435 Nonoperated Patients was made by Sven Hammarstrom (Stockholm) and Poul Bechgaard[1] (Aarhus Denmark) The patients who were operated on were followed two to eight years and included all hypertensives operated on at the Neurosurgical Clinic of Serafimer Hospital Stockholm from February 1940 to August 1946 except three who have not been traced Five patients died as a result of the operation Since 1943 there has been no operative mortality in a consecutive series of 250 hypertensives Bilateral lumbodorsal ganglionectomy and splanchnicectomy from the ninth thoracic to the first lumbar level according to Smithwick s method was done on 148 patients of these 24 later died Another 64 were operated on bilaterally according to Peet s method of these 13 later died In 31 patients operation was done on one side only 18 of these later died

Patients not treated surgically were selected according to the same rules as the surgical subjects and followed for 2 10 years

Patients were divided into four groups men and women were treated separately Group I was not included in this study as it contained patients with uncomplicated hypertensive disease and no marked subjective symptoms Patients with such benign hypertension were not selected for sympathectomy Group II included those with pronounced subjective symptoms but no signs of myocardial damage Retinal changes in this group were classified as group 1 or 2 according to Keith and Wagener Group III included patients with the same eyeground changes or in addition retinal hemorrhages with or without signs of thrombosis of retinal vessels These patients further showed one or more of the following signs of cardiovascular damage negative T_1 in the electrocardiogram heart volume above the predicted normal resid

(1) Am J Med. 6 53 56 J ry 1950

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numbness of tongue lips and extremities carpopedal spasm and nausea Massage over the adrenal areas failed to produce any attacks Hyperventilation easily produced headaches carpopedal spasm and a rise in blood pressure from 184/122 to 244/150 Intravenous urograms failed to reveal any deformity or tumor Perirenal aerograms also failed to outline an adrenal mass Exploration through bilateral lumbar incisions revealed a normal right adrenal gland and a well encapsulated tumor the size of a large egg in the left adrenal area This was completely excised Recovery was complete and 18 months later the patient was entirely normal

Clinical attacks are the most impressive feature of the syndrome produced by pheochromocytoma Attacks last a few minutes to a few hours occasionally two or three days At onset of an attack palpitation is common with headaches and pain in the precordium or epigastrium and nausea and vomiting Anginoid pains epigastric pain roaring in the head occipital headache heat in the face and sneezing are other symptoms Blood pressure may be normal but is usually elevated between attacks Hyperglycemia and glycosuria occur in about one fourth of patients Thyroid enlargement and elevation of basal metabolic rate are not uncommon An unusually high incidence of generalized neurofibromatosis has been reported in pheochromocytoma

Pheochromocytomas originate from the chromaffin tissue system Chromaffin tissue is widely scattered Tumors have been reported to arise from the intrathoracic sympathetic chain from below the bifurcation of the aorta from the coccygeal body from the carotid body and in the wall of the intestine but none of these has produced the cardiovascular picture Only those in adrenal glands or in the retroperitoneal tissue between the kidneys have shown associated hypertension Tumors of all sizes have been reported varying from a few centimeters to melon sized masses They are sometimes malignant

Paroxysmal hypertension has been reported with adrenal ganglioneuromas with neuroblastomas and with adrenal cortical tumors In patients with pheochromocytomas attacks can sometimes be induced by hyperventilation by massage over the adrenal area or by changes in posture Histamine acid phosphate 0 1 cc of 1 1 000 given rapidly intravenously produces little effect in normal persons but in those with a pheochromocytoma may cause a severe paroxysm of hyper

ual damage after cerebral insult and constant albuminuria Group IV included all hypertensives with definite retinal exudates and/or papillary protrusion since life expectancy was found to be about the same whether papillary protrusion was or was not present

Prognosis was found to be consistently better in the patients operated on than in the controls In patients with retinal exudates (group IV) this difference was statistically significant in both sexes In groups II and III mortality rate was more than twice as high in men as in women In men with signs of cardiovascular damage (group III) prognosis was significantly better in those operated on than in the controls The lower mortality rate in group III women who were operated on compared with controls in this group was less significant but was still 60 per cent In group II patients life expectancy is favorable and a longer follow up is needed to decide if neurosurgical treatment significantly improved prognosis

Sustained Hypertension Due to Pheochromocytoma *Report of Case Cured by Removal of Tumor* is presented by *Hugh P Smith Jr R Bruce Logue and Donald E Beard*[2] (*Emory Univ*)

Man 23 was hospitalized complaining of headaches and weakness of the legs of approximately 18 months duration Symptoms had begun shortly after he had been rejected by the Army because of hypertension Headaches usually occurred when he wakened and were less severe during the day They recurred for two or three days and then did not appear for several more days Hot weather and physical exertion seemed to initiate them The patient also noted one to three day episodes of weakness in the legs

On admission blood pressure was 240/124 Examination revealed no abnormality except extreme constriction of the retinal arterioles without hemorrhages or exudates a slightly enlarged heart with a grade I systolic murmur at the apex and frequent extrasystoles White cell count was 17 800 In 14 urine specimens specific gravity varied from 1 002 to 1 012 Urinary output averaged 3 000 4 000 cc daily A trace of sugar was noted in the urine on one occasion An electrocardiogram showed left ventricular hypertrophy

Amytal® sedation lowered blood pressure from 190/112 to 154/94 Cold pressor test showed practically no rise Tetraethyl ammonium chloride caused no significant change in blood pressure When 0 037 mg histamine base was given intravenously blood pressure fell immediately from 205/130 to 136/70 then rose precipitously to 260/146 the reaction was severe—flushing hyperventilation

( ) C eol t on 3 454 460 M rch 1950

impressions of the patient s sensorium and ophthalmoscopic observations of eyegrounds suggest that these areas receive adequate circulation during hypotension

Wilkins observed the effect of V viride in two small groups of patients Vertavis* was administered to 34 patients for 1 13 months Eleven per cent had a lowering of 50 mm or more and 70 per cent a lowering of 20 mm or more in average systolic pressure 14 per cent had a decrease of 30 mm or more and 41 per cent a decrease of 20 mm or more in average diastolic pressure Similarly in 20 patients to whom an experimental drug veriloid was given for 6 20 weeks average systolic pressure was reduced 50 mm or more in 30 per cent and 20 mm or more in 70 per cent and diastolic pressure 30 mm or more in 50 per cent and 20 mm or more in 70 per cent In both groups arterial pressure was rarely restored to normal Associated symptoms and signs of hypertension in general were favorably affected or at least remained unchanged On continued administration there was no evidence of development of tolerance or idiosyncrasy to the drug

Patient and physician must co operate to establish a symptom free therapeutic dosage schedule Moreover dosage requirements may vary considerably from patient to patient so that only by cautious trial of increasing doses can the proper schedule be established The most satisfactory mode of administration is by mouth after meals and at bedtime

Although V viride in present available forms is far from an ideal or curative medicinal agent in essential hypertension further investigation of purified products without objectionable side effects is justified

Clinical Studies on Veratrum Alkaloids Action of Protoveratrine and Veratridine in Hypertension Clinical use of veratrum alkaloids has fallen into disrepute mainly for two reasons Alkaloid content of the plant extracts vary greatly and reliable standardization methods are not available Veratrum causes severe toxic reactions such as nausea vomiting and unpredictable sometimes profound fall in blood pressure Despite these drawbacks certain obstetric clinics have continued to use Veratrum viride in eclampsia Recently there has been a revival of use of the drug in treatment of hypertension

Edward Meilman and Otto Krayer[4] (Harvard Univ) in

(4) C cul t 1 04 213 F bru y 19 0

tension after the initial fall in blood pressure Tetraethyl ammonium chloride and the adrenolytic benzodioxane drugs have also been recommended as test substances Both should lower high blood pressure caused by circulating epinephrine

Operation is not without danger There is an increased susceptibility to paroxysmal tachycardias and to auricular or ventricular fibrillation in the presence of excess epinephrine Patients often show a great rise in blood pressure when the tumor is being manipulated and a great fall after veins from the tumor are ligated For this reason adequate amounts of epinephrine and adrenal cortex extract should be available Possibly benzodioxane drugs could be used to prevent exces sive rises in blood pressure due to manipulation of the tumor at operation

Veratrum Viride and Essential Hypertension are discussed by Robert W Wilkins[3] (Boston Univ) Although Veratrum viride has been used intermittently for more than a century in treatment of fever tachycardia and disturbances of the cir culatory system in modern times its use has been generally discredited Recently however it has been tried clinically in essential hypertension with results favorable enough to stimu late physiologic studies of its hemodynamic effects in man

Hypotensive effects of V viride whether crude root puri fied extract or pure alkaloid are apparently similar in normal animals normal persons and hypertensive patients Generally vasodilator these effects may be mediated through the cen tral nervous system Salivation nausea and vomiting are the most frequent of the unpleasant side effects circulatory col lapse is the most alarming though usually innocuous evi dence of overdosage of the drug As antidotes for these re actions atropine (0 5 1 0 mg) or ephedrine (30-45 mg) or both have been given intramuscularly During the hypoten sive response to V viride cardiac output does not decrease but on the contrary may increase In no sense sympatho lytic the drug leaves vasomotor reflexes and postural adapta tions intact Although renal blood flow initially may decrease with the first appreciable fall in arterial pressure after admin istration of the drug it returns to control values when the pressure becomes stabilized at lower levels Although blood flow through the brain has not yet been measured clinical

(3) New E gl nd J Med 4 535 538 Ap 6 1950

In 168 trials with protoveratrine first degree heart block occurred 4 times nodal rhythm 12 times ventricular extrasystoles 2 times bigeminy 2 times and Wenckebach phenomenon twice Arrhythmias appeared about 10-15 minutes after injection and usually lasted a few minutes If the dose which produced arrhythmia was given simultaneously with atropine no arrhythmia appeared yet blood pressure did fall Patients who were fully digitalized showed electrocardiographic changes such as increased P R interval or bigeminy at lower doses of protoveratrine

With veratridine only slight or no fall in blood pressure or heart rate occurred at doses that produced nausea vomiting and sweating except in one patient

It is concluded that protoveratrine in a dosage range causing satisfactory clinical circulatory effects has insignificant side effects or none at all Veratridine in the authors opinion scarcely warrants further clinical trial Upper range of dosage of protoveratrine for therapeutic application is not definitely established and it is an exceedingly toxic drug

Influence of Sodium Chloride on Actions of Desoxycorticosterone Acetate Attention has repeatedly been called to the fact that many toxic actions of desoxycorticosterone acetate (DCA) depend on sodium chloride content of the diet Excessive dietary supplements of sodium chloride increase severity of the nephrosclerosis periarteritis nodosa and hypertension produced by DCA treatment whereas diets comparatively poor in sodium chloride tend to diminish these toxic reactions Hans Selye Helen Stone Paola S Timiras and Carlos Schaffenburg[5] (Univ of Montreal) report an additional series of observations on rats receiving DCA while on a diet completely devoid of sodium chloride Experiments were performed to determine whether dietary protection against DCA is absolute or relative and whether it extends to all actions of the corticoid or is limited to some of them

Unilaterally nephrectomized rats were divided into two groups One was untreated In each animal of the other group two 40 mg pellets of DCA were implanted All animals were given a synthetic sodium chloride free diet for four weeks At this time each group was divided in half and half the animals in each of the original two group were given 1 per cent

(5) Am H rt J 37 1009 1016 J 1949

jected protoveratrine intravenously 168 times in 26 hypertensive patients The highest single intravenous dose was 0 20 mg Veratridine was administered to 14 patients 17 times intravenously and 7 times intramuscularly

Fall in blood pressure produced by protoveratrine was essentially the same each time and was usually maximal in the first 10 15 minutes Results were similar in patients with renal hypertension and those with essential hypertension Amount of protoveratrine which caused a given fall in blood pressure varied from patient to patient In general doses of 1 μg/kg or less had little or no effect Above this level and up to 3 μg/kg there was increased response with increasing doses Larger doses were not tested Duration of action was variable but was usually one to three hours depending on dose as well as on the patient Fall in blood pressure was accompanied by a decrease in heart rate which could be abolished by atropine Response to the cold pressor test was not abolished during the hypotensive period following administration of protoveratrine In more than half of 40 experiments a moderate postural hypotension occurred affecting systolic level more than diastolic pressure

In every instance intravenous administration of a large enough dose of protoveratrine produced a subjective sensation of unusual warmth in the face mouth throat hands epigastrium perineum and feet which was not unpleasant and lasted 10 25 minutes With the highest doses given there was frequently slight dizziness aggravated by quick motions of head or eyes In five patients large doses caused a pressing choking sensation in the epigastrium and substernally with a tendency to deep sighing respirations Neither of the two patients with angina pectoris in the series experienced this substernal oppressive feeling after the drug however Five patients were given protoveratrine while suffering from headache One did not respond in two there was mild relief with fall in blood pressure and in two a severe headache was completely alleviated during the hypotensive period

Four of eight patients who had the pattern of left axis deviation with flat or inverted T_1 had reversion of T_1 to upright during the period of lowered pressure and a return of the upright T wave to a flat or inverted wave as the effect of the drug wore off and blood pressure rose to previous levels

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(5) Am Heart J 37 1009 1016 J 1949

saline to drink other animals remained on the sodium chloride free diet The experiment was continued for another five weeks at the end of which time moribund condition of DCA treated animals receiving saline made it necessary to terminate the study

Results showed that rats maintained on the sodium-chloride free synthetic diet tolerated otherwise fatal doses of DCA Sodium chloride deficiency also prevented renal and cardiac enlargement nephrosclerosis myocarditis hypertension and periarteritis nodosa *normally* caused by excessive amounts of DCA however it did not prevent atrophy of the adrenal cortex and pituitary which results from overdosage with this corticoid

From these observations the authors conclude that sodium is essential for the renal and through the intermediation of the kidney for the cardiovascular actions of DCA

Production of Hypertension in Rat by Substituting Hypertonic Sodium Chloride Solutions for Drinking Water is reported by Leo A Sapirstein Wilbur L Brandt and Douglas R Drury[6] (Univ of Southern California) In three experiments systolic blood pressures were determined in 27 control rats and in 31 rats whose sole source of fluid was 1 5 2 5 or 2 per cent sodium chloride solutions for six weeks In animals watered with hypertonic saline solutions arterial hypertension developed after a latent period of one to four weeks Autopsy revealed this to be associated with hypertrophy of the heart and kidneys relative to body weight The authors concluded that substitution of hypertonic sodium chloride solutions for drinking water affords a simple inexpensive and dependable method of producing arterial hypertension in the rat

Importance of Dietary Protein Calories and Salt in Experimental Renal Hypertension Philip Handler and Frederick Bernheim[7] (Duke Univ) report on data obtained in control experiments preliminary to studies of the significance of liver function in renal hypertension Purified synthetic diets were used in study of effects of various nutritional factors on blood pressure of adult male rats rendered hypertensive by subtotal nephrectomy Dietary levels of protein calories and salt

(6) Proc Soc Exper Biol & Med 73 8 85 January 1950
(7) Am J Physiol 160 31-40 January 1950

independently exerted a profound influence on systolic blood pressure

Effect of protein was determined at three dietary levels all of which supported rat growth In rats ingesting diets of normal salt content systolic pressures were stabilized at the following levels high protein 168 mm medium protein 145 mm low protein 122 mm Addition of urea to a low protein ration exerted a slight pressor effect but not sufficient to account for the observed effects of dietary protein Addition of tyrosine and phenylalanine in amounts present in a 50 per cent casein diet had no effect on blood pressure

Restriction of daily food consumption to an amount just adequate for weight maintenance or very slow growth resulted in a fall to virtually normal pressures on all diets but that containing an unusually excessive amount of salt Drastic reduction of sodium content of the diet only slightly reduced systolic pressures of rats on high protein rations Addition of 3 per cent sodium chloride (10 times the normal level) to a low protein ration resulted in pronounced hypertension

It cannot be stated whether hypertension created in this fashion is analogous to any type of hypertensive disease known to occur in man In any case if results of this study are applied to management of hypertensive disease in man only qualitative concepts may be justifiably utilized

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CORONARY ARTERY DISEASE

Recent studies suggest that the ballistocardographic technic may become a valuable adjunct in the diagnosis of angina pectoris Further investigations will be awaited with interest

The symptomatic benefit derived from coronary dilators is well known Although there is as yet no proof that these drugs have a beneficial effect in the disease by favoring the development of collateral circulation the clinical evidence is suggestive A controlled study of this problem utilizing a large number of patients would be of much interest.

The last article in this chapter would suggest that when done cautiously and with due regard for the dangers of pulmonary edema intravenous infusion may be a valuable emergency measure in treatment of the state of circulatory collapse brought on by myocardial infarction —Ed

Ballistocardiographic Findings in Patients with Symptoms of Angina Pectoris are reported by Herbert R Brown Jr Marvin J Hoffman and Vincent de Lalla Jr[8] (Univ of

(8) Circulation 1 13 140 J[illegible]y 1953

Rochester) A new aid in the diagnosis of angina pectoris is *the ballistocardiograph an instrument which records waves* arising from the heart beat itself when the pulse impact of ejected blood strikes the arch of the aorta pulmonary arteries and peripheral vessels

In a series of 50 patients 26 were thought to have typical angina pectoris and 24 atypical Patients were excluded from the series if they had symptoms of aortic stenosis aortic regurgitation hypothyroidism hyperthyroidism acute or chronic pulmonary disease anemia or arrhythmias or positive reactions for syphilis Abnormal ballistocardiographic changes were demonstrated in all 26 patients with typical angina pectoris 21 of whom had objective cardiac abnormalities and 5 of whom did not Of 24 patients with atypical angina pectoris 21 showed varying degrees of ballistocardiographic abnormality although only 11 of the 21 had one or more of the usual stigmas of cardiovascular abnormality The three remaining patients had no objective evidence of cardiac abnormality and had normal ballistocardiograms therefore *they were thought to be in anxiety states* Since *in all but 3* of the 50 patients the clinical diagnosis of angina pectoris was supported by abnormal ballistocardiograms ballistocardiography is considered to be a helpful diagnostic aid especially in atypical cases

Because the duration of symptoms in atypical cases was *17 3 months compared to 39 2 months* in typical cases it was inferred that many patients with coronary artery disease may have atypical complaints preceding the development of classic *and easily recognizable symptoms A considerable number of* patients may present no signs or symptoms although they may have a moderate degree of arteriosclerosis of the coronary arteries In this category is the patient who ultimately has an acute myocardial infarction but who never had a sick day or a pain in his life In *supposedly healthy* patients over 50 abnormal ballistocardiograms are *not* surprising considering the incidence of heart disease although other criteria may often be negative many asymptomatic or atypical patients should curtail activity *The ballistocardiograph* furnishes objective evidence of circulatory abnormality in such cases by revealing defective mechanical heart action

Blood Cholesterol Studies in Coronary Artery Disease are

reported by Morris F Collen[9] Abundant evidence has accumulated which shows that most patients with coronary artery disease have a sustained hyperlipemia In a series of 84 male patients with acute myocardial infarctions the average plasma cholesterol concentration was 297 mg/100 cc Fifty two per cent had cholesterol levels over 300 mg By contrast in 66 normal subjects (persons who were not overweight and showed minimal evidence of aging) the average cholesterol level was 249 mg and only 10 per cent had cholesterol concentrations over 300 mg In general patients who had had an acute myocardial infarction at a young age tended to have a higher plasma cholesterol level than those who had had an infarct late in life

Plasma Cholesterol Concentrations Following Ingestion of 5 Gm Cholesterol in Patients with Coronary Artery Disease Morris F Collen David De Kruif and Frederick Geier[1] measured plasma cholesterol and ester concentrations in patients while they were fasting and two and four hours after ingestion of a test meal consisting of 250 Gm fresh egg yolk (about 5 Gm cholesterol) Determinations were performed on 27 normal adult males i e persons without evident metabolic disorders and with a negative family history for coronary artery disease and on 53 male patients who had recently had an acute myocardial infarction and therefore presumably had coronary atherosclerosis

Criteria for a normal cholesterol tolerance test were (1) an initial fasting cholesterol level below 300 mg/100 cc plasma and a cholesterol ester level below 200 mg (2) changes in plasma cholesterol concentrations two and four hours after the test meal which did not increase above the fasting levels by more than 30 mg cholesterol or 20 mg cholesterol esters According to these criteria 60 per cent of the 27 normal adult males had normal tests Ninety per cent of the 53 male patients who had recently had an acute myocardial infarction had abnormal tests in that one or more of the above criteria was exceeded

Coronary Sclerosis as Symptom of Xanthomatosis Muller s Syndrome The assumption that an increased amount of cholesterol in blood is an important factor in pathogenesis of

(9) P m Fou l M B ll 7 55 59 J ly 1949
(1) Ib d pp 60 66

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Comparative Studies of Effect of Some Vasodilators in Angina Pectoris are reported by Ebbe Nyman[3] (Karolinska Hosp Stockholm) Defective knowledge regarding the quantitative effect of the different vasodilator drugs in man under physiologic and pathologic conditions is partly to be explained by the lack of objective reproducible functional tests that has hitherto existed The calibrated and reproducible tests for cardiopulmonary function now available allow more satisfactory study of this question

The cardiopulmonary function test used in the present investigation consisted in measured work on a bicycle ergometer Moderate work of 600 kg/minute was used An electrocardiogram was made after four minutes work and again three minutes after work was concluded The various vasodilators were then given and time of appearance of pain during work on the ergometer under influence of the drug was compared with time of appearance of pain in a control test before medication The whole series of experiments was carried out within one month and the tests were made at the same time each day on a man 35 who had had angina pectoris pains with typical localization and radiation in connection with rapid walking running and bicycling uphill for about four years There were no physical or roentgen signs of organic heart disease or of sclerosis or thromboangiitis obliterans in peripheral vessels

Best effect both on duration of pain free working period and the ECG was obtained with administration of a drug with a rapid action shortly before start of the function test Nitroglycerin 0 5 mg orally doubled length of the pain free period and had a noticeably favorable effect on the ECG Theophylline with ethylenediamine 0 24 Gm administered intravenously also prolonged the pain free period considerably and the ECG was likewise influenced favorably Theophylline with ethylenediamine 1 8 Gm orally also had a good effect on the pain free period but effect on the ECG was not so striking Sorbide dinitrate 0 09 Gm by mouth prolonged somewhat the pain free period but did not cause any change in the ECG Papaverine hydrochloride 0 03 Gm intravenously improved the ECG but did not alter duration of the pain free period Procaine 0 30 Gm over the

(3) Acta med Scand 131 565 570 1948

arteriosclerosis has been supported by experimental investigations in which rabbits fed cholesterol developed lesions of the arteries similar to those observed in human arteriosclerosis This experimental arteriosclerosis has a direct parallel in the systemic disease xanthomatosis which is associated with an increased amount of cholesterol in blood

Xanthomatosis is characterized by hypercholesteremia and abnormal cholesterol deposits in various organs especially in skin tendons and intima of arteries Cutaneous manifestations appear as flat or tuberous nodules Epidermis is always unaffected but the yellow color of underlying cholesterol deposits may be seen if skin is stretched On eyelids deposits appear as xanthelasmas Tendinous xanthomas are most often found on extensor tendons of fingers back of hands or below knuckles elbows tibial tuberosities and on the Achilles tendons Vascular deposits appear as typical atheromatous plaques in intima of aorta coronary arteries and larger arteries of the legs In advanced stages changes are macroscopically the same as in severe arteriosclerosis Xanthomatosis is a distinct hereditary disease apparently transmitted in a dominant way

Gunnar Welin (Gothenburg Sweden) describes a family of four brothers and three sisters six of whom showed pathognomonic external xanthomas between the ages of 29 and 47 Localization consistency and size of xanthomas of the different members showed a remarkable similarity All but one had symptoms of coronary sclerosis (angina pectoris) and two died of sudden cardiac failure In the two oldest brothers electrocardiograms showed changes significant of old posterior infarction The oldest brother died suddenly two months after examination autopsy showed a severe atheroarteriosclerosis which did not present any definite peculiarities The statement that it is impossible to differentiate between xanthomatous arteriosclerosis and arteriosclerosis of other origin at autopsy is thus confirmed Blood cholesterol was determined in five of the patients and two of their children All siblings and one of the children had definite hypercholesteremia with serum cholesterol values above 3̄0 mg per cent

( ) Act med Scand a 134 53 60 1949

more apt to experience greater hypotension and other unpleas ant side effects The optimal dose for each patient was deter mined by beginning with small intravenous doses (50 or 100 mg) and working up to optimal dose

In this small series no conclusions could be drawn as to beneficial results other than symptomatic improvement However especially in patients for whom other methods of treat ment proved inadequate the additional relief obtained with TEAC was gratifying

So called Silent Myocardial Infarction It has long been recognized that certain cases of myocardial infarction occur apparently without pain and that dyspnea is the predominant symptom and may overshadow the sensation of pain in the clinical picture Recently considerable evidence has indicated that prompt institution of anticoagulant therapy in acute myocardial infarction results in a diminished degree of mor bidity and possibly also in a diminished mortality rate Hence ready recognition of forms of this disease in which pain is not a prominent feature has increased in importance Harold R Hipp James M Behrman and Howard E Heyer[5] (Dallas) attempted to determine conditions under which acute myo cardial infarction might occur without readily recognizable evidences of pain and also to determine in such cases subjec tive symptoms other than pain which might indicate occur rence of the acute disease

Histories of 150 cases of recent myocardial infarction were reviewed and in 11 no history of pain had been obtained Diagnosis in 10 of the 11 cases was confirmed by autopsy a relatively acute infarction being found in each The eleventh case was confirmed by evolution of a pattern of typical elec trocardiographic abnormalities

In the 11 cases the term painless proved to be a misnomer for in all there were factors which were probably sufficient to explain the absence of a history of pain The history was in adequate in five patients one was psychotic one in diabetic acidosis two were in deep diabetic coma and one also in coma was found at autopsy to have a cerebral embolus A poor history is probably the commonest cause for absence of a his tory of pain Another patient complained of sudden onset of asthma with fever This probably represented onset of

(5) Am P t 4 64 66 O t be 1949

sternum prolonged the pain free period shifted the pain higher up and had some effect on the ECG

Results do not permit far reaching conclusions However one fact that emerges is that a sure effect is achieved only if the drug being tried is given in a readily absorbable form in immediate connection with the function test With the possible exception of sorbide dinitrate relatively small peroral doses of the drugs with a slower action did not seem appreciably to increase functional capacity

Tetraethylammonium Chloride in Treatment of Angina Pectoris William J Atkinson Jr[4] (St Louis Univ) gave tetraethylammonium chloride (TEAC) for 1 20 months to 25 patients with angina pectoris In 25 patients symptomatic improvement occurred judged by decrease in number of anginal and allied attacks weekly and by an increase in exercise tolerance Of those who improved 65 per cent had a significant decrease in number of attacks and 60 per cent a noticeable increase in exercise tolerance Psychogenic effects of the decided sensory stimulus obtained with TEAC intravenously seemed to play a part in these benefits However this was thought merely a contributory factor since only 1 of 11 patients did as well on other drugs which gave a sensory stimulus

Of the 28 patients treated 65 per cent were followed 6 20 months No harmful effects attributable to administration of the drug were noted though most patients were over 60 and had either experienced a myocardial infarct before this study or had been in congestive failure at some time

Electrocardiograms of four patients taken before anginal attacks during an attack and two to four minutes after intravenous administration of TEAC showed an anginal pattern during the attack and reversion to the preanginal pattern immediately after administration of the drug Atkinson believes that TEAC actually breaks up the process involved in an anginal attack

Optimal dose of TEAC for treatment of angina pectoris varied greatly from patient to patient Responsiveness to the drug was usually increased by severe heart disease old age arteriosclerosis and some forms of hypertension If the dose was too large patients with one or more of these factors were

(4) Am Heart J 39 336 35 March 1950

the shoulder may atrophy The term shoulder hand syn drome has been given to this form of reflex dystrophy The reflex is thought to start from an area of local tissue disturb ance such as a traumatized extremity myocardial infarct or cerebral lesion Impulses from these areas set up a central disturbance in the nature of a widespread continuous agita tion of the internuncial pool which spread steadily to stimu late anterior and lateral horn cells This incessant stimulation is expressed peripherally by motor and neurovascular symp toms Muscle spasm and vasomotor imbalance result and pro duce characteristic clinical features of the shoulder hand syndrome Treatment is repeated stellate ganglion infiltration with procaine

In group 2 pain is referred to neck shoulder and upper extremity without trophic changes There is no pain on mo tion nor is movement of the shoulder joint restricted Pain is reflexly referred to (1) neck shoulder and proximal half of the upper arm or (2) neck shoulder and entire upper extrem ity with burning tingling and a sensation of numbness in hand and fingers Shoulder and arm feel heavy and tired the dorsum of the wrist may become sore and gripping power of the hand is often diminished Pain is usually worse at night Diffuse tenderness may be present The clinical picture is that of scalenus anticus syndrome The authors present a case with these features

Man 61 had experienced recurrent mild epigastric pain radiat ing up to sternum and left shoulder 18 months previously Eight months previou ly he had been hospitalized for syncope Diagnosis was arterio clerotic heart disease with cardiac enlargement coronary sclerosis and healed anterior myocardial infarct A second coronary attack *occurred three months later Five months after the second* attack the patient s chief complaint was pain in the left shoulder arm and hand particularly severe at night The left hand was numb and weak Examination revealed a tense tender scalenus anticus muscle on the l ft Pressure on the lower end of the muscle above the clavicle caused evere pain which radiated to the shoulder arm and hand reproducing and intensifying the patient s symptoms In jection of the scalenus anticus muscle with 1 5 cc of 2 per cent pro caine caused the pain to disappear Tingling and numbness disap peared and strength of grip was restored There was slight recur rence of pain two weeks later and injection was repeated

The authors suggest that the mechanism of the scalenus anticus syndrome following a myocardial infarct is a sensori motor reflex mediated by the phrenic nerve When a myo

substernal tightness which is a common symptom of in farction of the myocardium Since pain is a subjective expe rience it is not surprising that it is interpreted in different fashions by different patients Three of the 11 patients were on the surgical service at time of the infarctions In all three administration of narcotics about the time when in retrospect it was thought that infarctions had occurred may have masked pain from the infarction Also it has been shown that pain in one part of the body actually raises the threshold for perception of pain arising in another area That a history of pain is frequently not obtained in patients in whom myo cardial infarctions develop after operation has been noted bv many observers Two of the 11 patients complained chiefly of sudden onset of exacerbation of dyspnea and orthopnea and no history of pain was elicited during their hospitalization That manifestations of myocardial infarction may be chiefly those of congestive failure has been known many years How ever lack of history of pain is not necessarily synonymous with lack of pain In patients who have both pain and dysp nea dyspnea often seems to overshadow the sensation of pain and becomes the chief complaint Also the fact that many patients suffering from coronary artery disease characterize their distress as tightness or use some other unusual de scription of the sensation makes the unraveling of that symp tom from those of the complicating congestive failure difficult

From information gained from these 11 cases there is little to indicate that myocardial infarction is not essentially a pain producing lesion So many conditions mav obscure *pain in this disease that absence of a history of pain* should not be taken to mean the patient did not have pain or that he would not have had pain had not his threshold of pain percep tion been altered

Possible Mechanism of Postcoronary Shoulder Pain has been investigated by Bernard D Judovich William Bates and Maurice S *Jacobs*[6] *(Philadelphia) Reports indicate* that the syndrome of painful shoulder following coronary occlusion can be divided into two groups In group 1 trophic disturb ances develop with changes resembling periarthritis of the shoulder joint and motion becomes painful and limited Re ferred pain may be causalgic or burning and structures about

(6) Am J Surg 8 16 19 August 1949

ARTERIOSCLEROSIS

The first articl eparates sharply the only clini ally important type of arteriosclerosi namely atheromatosis from a number of benign and incidental arterial disea es which are often confused with the more serious process A strong case i made for the importance of mechan cal factors in determining the site of atheromatous change and of diet as a predispos ing factor in atheroma It i becoming increasingly clear that the level of blood cholesterol and apparently of certain lipoproteins of a special molecular ize is mportant in the production of atheroma The relative importance of total caloric intake fat intake and cholesterol intake a determinants of blood cholesterol remain in di pute The po sibility that the plasma concentration of certain lipoproteins with a specific migra *tion velocity rather than that of cholesterol is respons ble for the tendency* toward atheromatou degeneration is exciting and further studies will be awaited with intere t —Ed

Causes of Arteriosclerosis According to William Dock[8] (Long Island College of Medicine) hardening of the arteries occurs in four different ways One way consists of atrophy of the media and replacement of muscle and elastic fibers by collagen which occurs as a diffuse symmetrical process pro ducing wide long tortuous vessels such as are seen on the temples of many persons soon after they become adult and which become increasingly visible with age This change causes no decrease in lumen and hence does not produce vas cular accidents or insufficiency The second way hardening of the arteries occurs is by aortic mucinous degeneration cystic degeneration or medial necrosis which commonly precedes dissecting aneurysm and occurs more often in hypertensive hypothyroid subjects than in others The third way is by regenerative intimal thickening in arteries supplying tissues which decrease in bulk and functional activity with age This change is part of the vascular atrophy of disuse and is most striking in ovaries after the menopause and in brains in which disseminated focal cortical atrophy occurs because of neu ronal involution and death The fourth way is by the intimal change which causes all of the clinical manifestations of arteriosclerosis atheroma formation or atherosclerosis Be cause atheromas have been shown to be rich in cholesterol and have been produced in rabbits by feeding cholesterol there has grown up an impressive body of evidence that this lesion is due to deposition in the intima of cholesterol and its

(8) B ll New Y k A d M d 26 18 188 M h 1950

cardial infarct takes place the resultant pericarditis irritates the sensory endings of the phrenic nerve This in turn causes an intrasegmental reflex reference of pain in the neck shoulder girdle and proximal half of the upper arm If stimuli are adequate a spasm of the anterior scalenus muscle develops as a reflex possibly axonal in mechanism Symptoms are then referred to the lower arm and hand by a reflex scalene spasm superimposed on the primary source of pain

Plasma and Blood Infusion Following Myocardial Infarction John J Sampson and Isadore M Singer[7] (San Francisco) gave 30 intravenous infusions of blood and normal human plasma to 11 patients exhibiting one or more shocklike episodes after acute myocardial infarction Whereas only 1 of the 11 patients recovered and was discharged asymptomatic results of the infusions appeared to have carried four patients over critical periods of hypotension and they died later of secondary infarction or heart failure

No apparent harmful effects of infusion of blood or plasma were demonstrated except in a single patient with a high initial venous pressure Infusions seemed to be more effective when systolic blood pressure was under 85 mm Hg They were likewise more effective when given before four hours after severe hypotension developed and at rates of at least 2 and preferably 2 5 5 ml minute

It is assumed that use of blood or plasma infusions probably cannot alter the immediate destruction of the myocardium by ischemia and that death will follow such destruction when it is extensive However the favorable effects may be due to (1) reduction of effects secondary to shock (improved irrigation of the coronary bed) (2) maintenance of normal or excess venous return to the heart to preserve cardiac output in the presence of the dilated left ventricle (3) reduction of the area of dilatation of the myocardium surrounding the infarcted zone a process which may possibly cause or increase the shocklike symptoms and hypotension

It cannot be predicated that all the successful results in this study were due to infusions since spontaneous recovery from hypotension after myocardial infarction is common However prompt response in most instances seemed conclusive evidence of a genuine therapeutic effect

(7) Am Heart J 38 54 68 July 1949

Africa remains unanswered The high cholesterol content of diets was thought to be a factor but in three separate studies in America no relation could be found between blood cholesterol and the cholesterol content of diets The importance of obesity in causation of atherosclerosis however has been well demonstrated Over most of the world want is the rule and atherosclerosis is being prevented where luxurious diet prevails atherosclerosis flourishes

Role of Lipids and Lipoproteins in Atherosclerosis Though some workers claim that most patients with atherosclerosis show a significant elevation in blood cholesterol level a considerable number have levels in the accepted normal range John W Gofman Frank Lindgren Harold Elliott William Mantz John Hewitt Beverly Strisower Virgil Herring (Univ of California) and Thomas P Lyon[9] (San Jose Calif) therefore undertook a physicochemical investigation of the giant molecules of serum which may be composed of cholesterol its esters phospholipids fatty acids and *protein as building blocks The basic premise was that it is* possible that a defect might exist in certain of these giant molecules which could be responsible for development of atherosclerosis whereas the mere analytic levels of any of the building blocks in serum might be of little or no significance

The serum of normal rabbits showed a lipoprotein which ultracentrifugally appeared as a single component of flotation rate between 5 and 8 Svedberg units under the experimental conditions used When these rabbits were fed 3 Gm cholesterol a week an increase in concentration of the previously existing 5 8 S_f component occurred and several new components of S_f class 10 30 appeared The number of new components appearing in the serum of individual rabbits varied from none to all despite the fact that the maintenance ration of cholesterol was the same for all animals When autopsy was done on rabbits after 15 weeks of cholesterol feeding it was found that those rabbits failing to develop high levels of the components of S_f greater than 5 8 units showed no gross atherosclerosis whereas mild to severe atherosclerosis developed in those with high concentrations of molecule of the S_f 10-30 class The observation that all rabbits attained comparable levels of the 5 8 S_f component but showed widely varying

(9) S 111 166 171 F b 17 1950

esters and to the resulting mild foreign body type of granuloma formation and scarring Thus it is similar to xanthoma which develops in the skin of persons with elevated blood cholesterol levels Dock believes that every patient with xanthoma has atheromas

Local factors in connective tissue are thought to play a large role because xanthoma and atheroma are focal lesions with an obvious predilection for certain sites the upper lids being the commonest location for xanthoma and the aorta near its bifurcation and the coronary arteries being the preferred site for atheroma There is striking evidence that atheromas develop only when the ratio of cholesterol to phospholipid exceeds a certain level Xanthomas form rapidly when the plasma cholesterol levels are high they never form when the blood cholesterol is 160 mg per cent or less Cholesterol precipitates in areas of necrosis hemorrhage or simple degeneration of the intercellular matrix So far however, there is little evidence that such degeneration or injury precedes cholesterol deposition in skin Xanthomas appear where connective tissue is in constant motion or vibration The anterior mitral leaflet and the epicardial parts of the coronary arteries usually the first sites of atheroma formation are also in constant motion A striking example is in arteriovenous fistula in which the artery leading to the leak shows far more atherosclerosis than the corresponding vessel on the opposite side of the body In such an artery the thrill or vibration due to flow of high velocity is greater than normal Thickness of the intima seems to be important also Coronary arteries have a far thicker intima than mesenteric or radial arteries and far more atheromas The rate at which plasma filtrate is forced into the intima is thought to depend on arterial pressure Atherosclerosis is definitely correlated with level of arterial pressure in both systemic and pulmonic circuits Tibial arteries have far more severe sclerosis than radials and the aorta at its bifurcation may be one confluent mass of advanced atheromas when the arch is the site of only a few small plaques Pulmonic hypertension predisposes to pulmonic atherosclerosis

The question of why atheromas appear in Europeans and North Americans even though they are normotensive and free from endocrine disease and not in the people of Asia or

Cholesterol Metabolism in Health and Disease Its Relationship to Arteriosclerosis is summarized by L N Katz J Stamler and L Horlick[1] (Michael Reese Hosp) Cholesterol metabolism is difficult to analyze because of the ubiquity of cholesterol and the complexity of its exogenous endogenous circulation Detailed solution must await intermediary metabolic studies in vitro and in vivo such as have been carried out with carbohydrate metabolism Tracer methodology utilizing isotopes must be extensively applied to this problem With this technic it has been shown that cholesterol is the parent substance of physiologically important steroids such as cholic acid and progesterone Presumably steroids of the adrenal cortex are also synthesized from the cholesterol molecule Tracer studies have proved synthesis of cholesterol from acetate Cholesterol homeostasis may also be studied by means of a tolerance test similar to that used for glucose

Plasma total cholesterol levels in normal persons show a wide variation from 107 to 320 mg /100 cc which is not significantly affected by age sex national or ethnic origin or climate Apparently normal diet also has no effect but this is still in dispute It has been shown that there is a complex plasma lipoprotein moiety involving all lipid constituents in relatively fixed proportions In normal postabsorptive plasma the lipid aggregates (chylomicrons) are 1 2 μ in size and the plasma is a clear limpid solution Disturbance of concentration and balance of lipids may lead to milky plasma (chylomicronemia) Lipid particles are less finely dispersed and their colloidal stability is less well protected This condition occurs physiologically after a fatty meal It is present in a number of pathologic states and has been implicated in pathogenesis of arteriosclerosis Ultracentrifuge studies indicate that atherosclerosis may be correlated with plasma level of particular low density cholesterol bearing lipoprotein molecules Presumably alterations in plasma lipid protein complexes lead to the ready precipitation of insoluble cholesterol and its esters either extra or subintimally Cholesterol esters remain entrapped in the arterial wall and by virtue of their irritant properties provoke growth of fibrous tissue and atheroma

Etiology and pathogenesis of nephrotic hypercholesteremia

(1) Am P ct 1 461 468 M y 1950

degrees of atherosclerosis suggests that this component is not implicated On the other hand correlation between development of severe atherosclerosis and presence in the blood of high concentrations of components of the S_f 10 30 class suggests that at least some of these components either are the molecules which deposit in atheromatous plaques or are a reflection in the blood of the metabolic abnormality which results in cholesterol induced atherosclerosis

Studies in man showed the incidence of measurable concentrations of molecules of the S_f 10 20 class to be significantly higher in males aged 20–40 than in females of the same age group Both males and females over 40 showed significant increases in the incidence of measurable concentrations of molecules of this class compared with corresponding younger age groups A higher incidence was found in diabetics than in normal persons of corresponding age groups Of 104 patients *with proved myocardial infarction 101 showed presence* of molecules of the S_f 10 20 class in measurable concentrations All these observations are considered compatible with the hypothesis that elevated serum concentration of these molecules is associated with development of atherosclerosis

Preliminary study of 20 patients whose diet was restricted in cholesterol and fats demonstrated that concentration of S_f 10 20 class of molecules was definitely reduced or even brought down to a level below resolution intracentrifugally in 17 within two weeks to one month

Comparison of blood cholesterol levels with presence or absence of molecules of the S_f 10 20 class revealed that although there is a general trend toward increased frequency of occurrence of such molecules in serums with cholesterols over 200 mg per cent this was by no means a universal finding It was quite common also to find serums with cholesterol levels well below 200 mg per cent with appreciable or high *concentration of molecules of the* S_f 10 20 class Further it was common to find serums with cholesterol levels well over 200 mg per cent without any measurable concentration of molecules of this class These facts are thought to explain why previous workers have been unable to reach definite conclusions concerning atherosclerosis by studying analytic cholesterol values

sis in man suggests that weight loss might account for the effectiveness of some procedures in preventing experimental atherosclerosis J B Firstbrook[2] (Univ of Toronto) investigated this possibility in the rabbit by examining the relation between weight changes produced by various levels of food intake and the severity of experimental atherosclerosis

TECHNIC—After preliminary observation for at least one week on Ralston Purina Rabbit Chow Checkers fed ad lib male rabbits of various breeds and unknown age were weighed and sorted on the basis of similar body weight into pairs or groups of three One animal in each group was allowed chow ad lib The other member of a pair was offered 50 per cent of the previous day s food intake of the freely fed animal The other two members of the groups of three were restricted to 60 and 40 per cent maximal intakes After two weeks on the restricted feeding schedule daily admini tration by stomach tube of 1 Gm cholesterol daily seven days a week was begun After four to even weeks cholesterol administration animals were killed and studied at autopsy

As expected there was a highly significant correlation between food intake and final weight In the absence of control of the other variables degree of atherosclerosis was not significantly correlated with cholesterol dosage with initial weight or with weight change Under conditions of this experiment variations in total cholesterol dosage had little effect

The authors conclude that in evaluation of agents suspected of influencing experimental atherosclerosis in the rabbit and probably in other species there must be statistical or experimental control of changes in body weight The low incidence of experimental atherosclerosis in rabbits rendered diabetic with alloxan before cholesterol administration is probably associated with characteristic emaciation of these animals rather than with a specific effect of the diabetes

Vascularization of Aorta Comparative Study of Aortic Vascularization of Several Species in Health and Disease J Schlichter and R Harris[3] (Michael Reese Hosp) using an injection technic studied the vascularity of the ascending aorta in the dog human chicken and rabbit roentgenologically and microscopically Re ults indicated that vascularity of the ascending aorta is comparatively greatest in the dog and decreases progressively in man the chicken and rabbit Species differences in number and distribution of vasa vaso

(2) S 3 31 33 J 13 1950
(3) Am J M S 218 610 615 D mber 1949

are unknown It is thought that the kidney plays an active role in lipid metabolism but specific aspects await elucidation Likewise cholesterol and thyroid hormone are intimately related physiologically but mechanisms of interaction are obscure Experimental feeding of large amounts of cholesterol has produced hypercholesteremia and atherosclerosis in certain species Lipotropic factors such as choline inositol methionine or lipocaic prevent fatty livers but do not consistently prevent hypercholesteremia and atherosclerosis

Plasma and tissue lipid pattern of cholesterol fed chicks is duplicated in man with primary xanthomatosis Unlike experimental cholesterol induced lipidosis however, this essential hypercholesteremia of man usually does not respond to a low fat diet or to lipotropic factors Victims of this disorder often succumb at an early age to coronary artery disease Atherosclerosis in diabetic subjects is thought to be secondary to hypercholesteremia The completely depancreatized diabetic dog exhibits marked hyperlipemia and hypercholesteremia A fatty liver develops Insulin abolishes the hyperlipemia but the fatty liver persists Addition of raw pancreas to the diet cures the fatty liver and restores plasma lipids to normal

In experiments with chicks the authors have shown that the degree of atherosclerosis is proportional to the amount and duration of cholesterol feeding They were unable to influence development of atherosclerosis by use of lipotropic substances It was possible with increased cholesterol intake to produce atherosclerosis despite minimal hypercholesteremia Desiccated thyroid was of value against cholesterol induced atherosclerosis in chicks but was ineffective in eliminating spontaneous atherosclerosis Action of thyroid was thought to be a specific effect on cholesterol and lipid metabolism the nature of which remains to be worked out

Obviously there are tremendous gaps in knowledge of cholesterol metabolism its disturbances and its relation to arteriosclerosis Since degenerative vascular disease is a principal cause of disability and death the closing of these gaps is of major concern

Effect of Changes in Body Weight on Atherosclerosis in Rabbit Evidence that a caloric intake in excess of energy requirement is associated with a high incidence of atheroscler

There was a wide spectrum of histologic changes resulting from prolonged cholesterol feeding ranging from increase in ground substance of the intima of the aorta with infiltration of sudanophile material to very extensive foam cell plaques hyaline and cartilaginous metaplasia and heavy deposits of calcium in granules and plates Cessation of cholesterol feeding was followed by fibrotic changes in lesions of both the thoracic and abdominal portions of the aorta by disappearance and diminution of foam cells and fat and by calcification of atheromatous abscesses Scavenger like fat filled cells were also noted in the intima

Controls showed few gross lesions but many microscopic ones Scattered focal deposits of sudanophile material were seen in the intima and inner portions of the media of the thoracic aorta In the abdominal aorta spontaneous lesions were characterized by fibrosis of the intima with sudanophile deposits and calcium granules at the intimal medial junction

Relationship of Atheromatosis Development in Chicken to Amount of Cholesterol Added to Diet Arteriosclerosis of a type closely resembling that found in man appears spontaneously with advancing age in birds The chicken possesses certain advantages for research in this field because atherosclerotic lesions can be induced in a relatively short time and the induced lesions resemble the spontaneously occurring ones in many respects Furthermore the chicken normally ingests cholesterol containing foods Spontaneous arteriosclerosis develops in the chicken at age 5 6 months at the earliest arteriosclerosis is found in 45 per cent of chickens over 1 year old It is obvious therefore that the chicken is a suitable animal for experimental production of atherosclerosis if used before age 6 months when spontaneous arteriosclerosis begins to occur

L Horlick and L N Katz[5] (Michael Reese Hosp) undertook to quantitate effect of various concentrations of dietary cholesterol on the rapidity and degree of development of atherosclerosis in the chicken Feeding of cholesterol in concentrations of 0 5 1 2 and 4 per cent of the diet for 5 10 and 15 weeks was investigated

Results showed a direct relationship between concentration of cholesterol in diet and frequency and severity of

(5) Am H t J 38 336 349 S pt mbe 1949

rum were unrelated to size of the aorta since vascularity the smaller dog aortas was superior to that of the larger ad human aortas whereas aortas of premature babies genera showed better vascularization than those of rabbits and chi ens of approximately similar size

These basic differences in blood supply in different sj cies may explain some of the difficulty in producing med necrosis or arteriosclerosis in dogs and the ease with whi these changes are produced in rabbits Correlation of t present findings with previous observations indicates th species with better vascular supply to the aortic wall ha less tendency to develop degenerative arterial lesions where species with poorer vascularity exhibit a greater tendenc

The hypothesis is suggested that development of dege erative arterial lesions appears to vary inversely with t blood supply to the arterial wall This hypothesis does n preclude the probability that other factors may play a role b emphasizes the importance of the blood supply factor

Retrogression of Atherosclerotic Lesions on Cessation Cholesterol Feeding in Chick Louis Horlick and Louis Katz[4] (Michael Reese Hosp) investigated the effects of ce sation of cholesterol feeding on the hypercholesteremia ar atherosclerosis resulting from moderate periods of cholester feeding

Prolonged feeding of a diet containing 2 per cent chole terol in cottonseed oil to chicks for 24 weeks resulted in pro gressive elevation of blood cholesterol levels There was in creasing severity of atherosclerosis for 15 weeks then a level ing off and a further increase in severity during the last weeks of the experiment Cessation of cholesterol feedin after 10 weeks caused a rapid decline in blood cholesterc levels to normal within 3 weeks There was also a gradua regression in severity of lesions over 14 weeks It appeare that early lesions could be completely resorbed on cessatio of cholesterol feeding whereas more severe lesions under went regressive and reparative changes There was little dif ference in rate of regression or disappearance of the aortic lesions in birds placed on a normal mash diet and those placed on a low fat cholesterol free diet after cessation of cholesterol feeding

(4) J Lab & Clin Med 34 14 7 144 Octobe 1949

medial necrosis or other degenerative lesions and so did not have the local ischemia or degeneration on which atheroma might be expected to develop Lesions in the two animals with atheroma were confined to the area of interference with the vasculature of the vessel wall Six dogs whose aorta was not cauterized were kept on a similar regimen of cholesterol and/or thiouracil They showed no atheromatous or other pathologic changes of the aorta The authors conclude that nourishment of the blood vessel walls may be one important factor in atheromatosis

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CONGESTIVE HEART FAILURE

A number of recent studies have emphasized the importance of sodium deficiency consequent to prolonged dietary restriction or to the injudicious use of mercurial diuretics It should be remembered that a patient may have an excess of extracellular fluid with edema in one part of the body and have extracellular fluid depletion in the remaining portions The symptom and management of this common disorder are indicated in one of the following articles —Ed

Experimental Hypervolemic Heart Failure Its Bearing on Certain General Principles of Heart Failure In a group of experiments by William Huckabee Gus Casten and T R Harrison[7] (Southwestern Med College) dogs were infused rapidly with large volumes of fluid Atrial and femoral venous pressures rose steadily during infusion cardiac output rose to a peak and then dropped The gradient of pressure along the veins decreased progressively during infusion These experiments indicated that the hemodynamic defect in primary hypervolemic heart failure is the heart s inability to respond to an increasing filling load beyond a certain point

From considerations concerned with the flow of fluids through tubes the authors conclude that the diameter of veins has more influence than venous pressure on volume flow and that the intact animal differs from Starling s heart lung preparation in that in the former peripheral resistance is variable and the diameter of the veins may vary This conclusion was illustrated by experiments in which only a rough correlation existed between venous pressure and cardiac output The authors suggest that the concept of inflow load in

(7) C cul t 1 343 356 M h 1950

atherosclerosis which resulted There was also a relation between duration of the feeding period and degree of atherosclerosis produced for each concentration of cholesterol in the diet With concentrations of cholesterol above 0 5 per cent increasing the feeding period beyond 10 weeks did not *appear to increase the amount of atherosclerosis* Atherosclerosis occurred as early as two weeks after beginning the diet Early occurrence of atherosclerosis was related to an enormous increase in blood cholesterol level which occurred during the first week of cholesterol feeding Amounts of cholesterol over 0 5 per cent produced much the same degree of hypercholesteremia suggesting that there was an upper threshold for assimilation of cholesterol There was a semi direct relationship between degree of lipemia and degree of atherosclerosis found

Occurrence of Atheromatous Lesions after Cauterization of Aorta Followed by Cholesterol Administration is described by J G Schlichter L N Katz and J Meyer[6] (Michael Reese Hosp) Disturbances in the vascularity of the aortic wall cause disease of the aorta In the dog obstruction of the vasa vasorum of the ascending aorta leads to medial necrosis and its sequelae aneurysm formation dissecting aneurysm and spontaneous rupture The tendency toward atheroma formation is thought related among other things to the state of the *vasa vasorum Vasa of the dog are extremely well developed* and this may be one reason for the known difficulty in producing atheromatosis in this animal In the present study on dogs therefore some of the vasa vasorum were destroyed and hypercholesteremia was superimposed for months The effect of this combination of procedures was *analyzed at autopsy*

The ascending aorta of eight dogs was cauterized In one atheroma developed within 20 weeks on being given cholesterol orally and intraperitoneally In a second dog atheroma developed within 12 weeks on the same regimen plus thiouracil orally In a third dog atheroma *failed to develop after* 10 months on cholesterol and thiouracil orally Three other dogs (two given cholesterol only and one cholesterol and thiouracil) lived less than five weeks postoperatively apparently not long enough for atheroma to develop The other two (one given cholesterol only and one thiouracil *only*) *did not show*

(6) Am J M. Sc. 218 603 609 December 1949

Energetodynamic Cardiac Insufficiency, discussed by Robert Hegglin[8] (Univ of Zurich) is characterized by a considerable lengthening of the QT space of the electrocardiogram associated with a shortening of the Q second heart sound interval verified on the phonocardiogram which is the expression of a prematurely interrupted ejection period This syndrome is caused directly by a disturbance of the metabolism of the myocardium the contraction of which becomes weak

Clinically this disturbance appears in all pathologic condition accompanied by hypopotassemia consequently in paroxysmal paralysis and grave and persistent diarrheas it is reversible and disappears completely after recovery from hypopotassemia But it appears also in many other pathologic conditions and thus acquires more clinical importance It is found in diabetic coma and in hypoglycemia in which there is probably also hypopotassemia because the potassium metabolism is nearly always disturbed in these manifestations in porphyria hyperthyroidism severe infections (pneumonia scarlet fever diphtheria and even some grave anginas) severe intoxications (barbiturates veratrine)

Diagnosis is easily made from the ECG and analysis of the heart sounds *In pronounced case auscultation reveals the* short interval between the first and second heart sounds The heart is not dilated or deformed Prognosis is good when the cause is removed at the opportune moment however death may be caused by the syndrome in the previously mentioned diseases

Since the syndrome is always found as a secondary complication of a general disease treatment must first be aimed at the primary disorder therefore the hypopotassemia must receive careful attention Administration of 1 5 Gm potassium chlorate by mouth corrects the situation in most cases

Surgical Treatment of 'Cardiac Lung' Ligation of Inferior Vena Cava and/or Tricuspid Valvulotomy To restore equilibrium between the two ventricles Pedro Cossio and Isidro Perianes[9] (Buenos Aires) have devised two operations One is intended to drain blood from the pulmonary venous system toward some sector of the systemic circulation by

(8) C d l g 15 65 77 1949
(9) J A M A 141 772 776 J ly 2 1949

corporating venous pressure and venous diameter should supplant that of venous pressure as the stimulus to changes in stroke output of the heart

Actual flow into the ventricle was thought to depend on the relation between inflow load and ventricular diastolic pressure Thus a decline in the latter function may occur when diminished peripheral resistance leads to increased systolic emptying and under such circumstances increased inflow and output occur with constant inflow load If ventricular diastolic pressure *rises inflow load must increase to keep inflow and* output the same In addition a rise of ventricular diastolic pressure occurs as a consequence of incomplete emptying of the ventricle and excessive residual blood This may occur not only when cardiac output is low but also when it is high It is suggested that the only hemodynamic disturbance constant to all types of heart failure is a reduction of cardiac output relative to inflow load

Hypervolemia may be either primary and a cause of cardiac failure or much more commonly secondary and a result of heart failure In states of myocardial failure rise in ventricular diastolic pressure necessarily results in a distributional shift of blood from the peripheral toward the central portions of the venous system

On the basis of these considerations the authors suggest the following physiologic classification of heart failure and other circulatory disturbances disorders of cardiac filling disorders of cardiac emptying and mixed types Disorders of cardiac filling include (1) deficient inflow (shock), (2) excess inflow with or without adequate systolic emptying (thyrotoxicosis anemia beriberi arteriovenous fistula acute nephritis and rapid infusions) and (3) mechanical interference as in pericarditis mitral stenosis and rarely ball valve thrombi or auricular tumors Cardiac emptying may be decreased because of (1) increased resistance (acute cor pulmonale aortic stenosis coarctation or hypertension) or (2) decreased myocardial function from cardiac arrhythmias or myocardial in*farction or* from inflammatory or degenerative myocardial disorders Mixed types include (1) unequal filling and emptying of separate heart chambers in valvular heart disease and (2) deficient filling and emptying of the heart in sodium depletion

lotomy failed in only one case in which the attempt was abandoned because of sudden collapse while the instrument was in the heart Two hours later the patient completely re covered but died a month later during an attack of pulmonary edema In each of the other four patients the operation proved relatively simple and venous pulse became positive and un dulating The patients were definitely improved one of them surviving the operation five months

TECHNIC—A hollow metal rod 2 3 mm in diameter and 30 cm long with a shallow hook at one end and a Hamilton manometer at the opposite end is inserted through a small incision in the jugu lar vein When the instrument enters the auriculoventricular orifice pulsations registered by the manometer increase in amplitude and as soon as it has passed through the orifice there is further sudden increase Once it has reached this position the instrument is gently advanced until resistance is encountered from the right ventricular wall then the instrument is turned outward and is drawn back to engage the chordae of the external cusp If they are successfully en gaged resistance is experienced Firm traction of the instrument sections whatever has been engaged by the hook The same pro cedure is repeated two or three times until a systolic murmur is heard to the right of the sternum The hook is then carefully with drawn

When the inferior vena cava was ligated above the venae hepaticae all animals died in one to three days of infarctions in the bowels and liver Ligation just below the renal veins gave satisfactory results Though the first attempt in a hu man being met with failure because of the patient s serious heart condition subsequent attempts brought both systolic and diastolic pressures down to normal and they remained so during two months the length of observation

Auricular Fibrillation without Other Evidence of Heart Disease Cause of Reversible Heart Failure Edward Phillips (Los Angeles) and Samuel A Levine[1] (Boston) investigated some of the changes in dynamics of the circulation that ap pear to develop as a result of auricular fibrillation in patients who have no other evidence of heart disease Their purpose was to emphasize that the arrhythmia alone can cause con gestive heart failure The clinical evidence also suggested that some cases of irreversible heart failure with auricular fibrillation may have started with an essentially sound heart and that the subsequent disability might have been prevented

(1) Am J M d 7 478 489 O t b 1949

end to end anastomosis of a large pulmonary vein with the axillary artery the splenic vein or the azygos vein The second is directed to reduction of the right ventricular output either by tricuspid regurgitation following a tricuspid valvulotomy or by reduction of the return of venous blood to the right side of the heart by ligation of one of the main veins

Drainage of pulmonary venous blood into the systemic circuit was not feasible however in experimental animals because pulmonary vein pressure was lower than systemic vein pressure Though pulmonary venous pressure is undoubtedly elevated in patients with heart failure another difficulty that precluded this operation in human beings was the large thoracotomy wound and prolonged general anesthesia which would not have been tolerated by patients in an advanced stage of cardiac disease On the other hand both tricuspid valvulotomy and ligation of the inferior vena cava were well tolerated Both procedures attained the contemplated objectives reduction in volume of right ventricle output subsequent decrease of the passive congestion of the lungs and consequently improved left ventricle efficiency identical with the effect of venesection but giving more lasting results Ligation of the inferior vena cava was a much more serious operation than tricuspid valvulotomy since it required a general anesthetic and produced postoperative disorders However it was more effective for the following reasons the surgeon could see what he was doing the operation was in itself a prophylactic measure against pulmonary embolism which so often causes death and it overcame the 50 per cent increased output caused by supine posture For half a century it has been known that lesions of the tricuspid valve far from aggravating a mitral lesion exerted a healthy effect thereon In the authors opinion surgery for the medically uncontrollable cardiac lung should begin by ligation of the inferior vena cava and be followed by tricuspid valvulotomy unless there are extensive vascular obstructions in the limbs that would render the first operation useless In mitral stenosis it is probably most satisfactory to undertake valvulotomy initially

Tricuspid valvulotomy was carried out in five patients four of whom had uncontrollable heart failure The fifth though relatively healthy was suffering from recurrent attacks of pulmonary edema despite intensive treatment Valvu

It is concluded that auricular fibrillation per se may produce cardiac dilatation and progressive congestive failure in patients with otherwise normal hearts This is a truly reversible type of heart failure There is reason to believe that a considerable number of patients with auricular fibrillation cardiac enlargement and congestive failure (that eventually becomes irreversible) have little or no organic heart disease The authors believe that regularization of the rhythm with quinidine in the early stages may prevent progressive heart failure and in the latter stages may be curative

Clinical Report on Toxicity of New Mercurial Diuretic (Thiomerin®) for Subcutaneous Administration Considerable effort has been directed toward developing a mercurial diuretic which is systemically less toxic than those previously used locally nonirritating and readily administered Recently the disodium salt of N(γ carboxymethylmercaptomercuri β methoxy) propyl camphoramic acid (thiomerin®) has been introduced for subcutaneous use This compound shows chemical similarity to mercurophylline (mercuzanthin®) but the theophylline has been replaced by sodium mercaptacetate with the formation of a mercaptide Cardiac toxicity in experimental animals has been reported to be about 1/160 that of other mercurials given intravenously

Alan R Feinberg Julien H Isaacs and William S Boikan[2] (Univ of Illinois) report clinical experiences with thiomerin® Two groups were studied 59 hospitalized patients and 350 outpatients een at intervals of one to four weeks The clinic group consisted entirely of patients with various degrees of congestive heart failure most of the hospitalized group were also in congestive failure Thiomerin® was administered subcutaneously in doses of 0 5 3 cc equivalent to 0 07-0 42 Gm of the compound or 0 02 0 12 Gm mercury The most common dose was 1 cc Hospitalized patients received 1 35 injections at intervals of one to three days clinic patients 1 25 injections at intervals of one to four weeks as determined by response

Results were evaluated by weight loss and clinical improvement Achievement of dry weight was used as a measure of effective diuresi Diuresis was satisfactory in the outpatient group Dietary co operation was found necessary

(2) Am J M S 218 298 301 S pt mb 1949

if normal rhythm had been restored by use of quinidine in early stages of the arrhythmia

Of the 84 patients studied all with auricular fibrillation of unknown etiology and no evidence of organic heart disease 61 had permanent fibrillation and 23 had transient fibrillation Forty seven patients were studied carefully before and after reversion of the arrhythmia with quinidine Six had pronounced congestive failure another patient who did not respond to quinidine also had congestive failure Seven others had latent congestive failure

The most common symptom of those without failure was palpitation In the group with failure there were the customary features of dyspnea orthopnea and an enlarged liver Transverse diameter of the heart averaged 14 4 cm during fibrillation and 14 3 cm after reversion in 20 patients without frank failure Transverse diameter in four with congestive failure averaged 17 4 cm during and 15 4 cm after auricular fibrillation In six patients the P R interval was slightly prolonged after reversion One of these reverted spontaneously without any medication Four patients showed transient inversion of T waves after reversion one of which reverted spontaneously without medication Vital capacity of lungs in 28 patients without failure averaged 3 448 cc during fibrillation and 3 700 cc after reversion In the group with failure the vital capacity increased from 2 575 to 3 725 cc Arm to tongue circulation time in 11 patients without failure averaged 24 seconds during auricular fibrillation and 20 seconds after regularization Venous pressure in 13 patients without failure averaged 107 mm H O during fibrillation and 97 mm after reversion

Regularization after quinidine therapy occurred in 88 5 per cent and there were no untoward complications In those who did relapse the normal rhythm persisted for an average of 26 9 months Average duration of regular rhythm in patients under 50 who relapsed was 61 4 months in those over 50 it was 21 months Nineteen patients had not relapsed and still had regular rhythm after 2 months to 21 years Maintenance of regular rhythm was much longer in these patients than in those with organic heart disease which was reverted In the group with advanced congestive failure responses were dramatic all symptoms disappearing after regularization

Thirty five ambulatory patients attending the clinic for severe congestive heart failure were given mercaptomerin sodium whenever a mercurial diuretic was clinically indicated The subcutaneous route was effective in removal of edema prevention of accumulation of edema and maintenance of the patient s state of compensation In this regard it was as satisfactory as the previously used diuretics given intravenously or intramuscularly

Thiomerin® was given to 73 hospitalized patients with the severest degree of chronic congestive heart failure In general diuretic response to the drug administered subcutaneously was as satisfactory as that to the previously used mercurial diuretics either intramuscularly or intravenously Local reactions were usually not clinically significant and none of the patients refused continuation of therapy because of local irritation

The authors concluded that mercaptomerin is an effective and safe diuretic which may be administered subcutaneously to advantage Predictability of a satisfactory diuretic response and degree of diuresis achieved are similar to those with intravenous use of mercurophylline injection Mercaptomerin sodium by subcutaneous injection is superior to other mercurial diuretics administered intramuscularly

Renal Failure Associated with Low Extracellular Sodium Chloride Low Salt Syndrome With the wide use of low salt diets in congestive heart failure and hypertension and with the often excessive use of dextrose in water for postoperative care renal insufficiency from the low salt syndrome may be more frequently observed Since it is usually unrecognized unless looked for specifically and since adequate replacement therapy will often alter an otherwise fatal outcome Henry A Schroeder[4] (Washington Univ) describes 21 cases of the condition and methods for its treatment

Development of the low salt syndrome was recognized by (1) successive depression of urinary volume occurring during three to five days (2) depression of urinary chlorides to negligible quantities (which did not increase after injection of mercurial diuretics) (3) rapid progressive gain in weight (4) elevation of nonprotein nitrogen content of the blood (5) fall in plasma levels of chloride and sodium and (6) occasionally an elevation of cardiac rate Symptoms complained

(4) J A M A 141 1171 4 S pt 10 1949

for maintenance of dry weight In 56 of the 59 hospitalized patients diuresis was equal to or better than that to be expected from other diuretic agents

Generalized toxic reactions were absent except for occasional development of muscle cramps fatigue and weakness resulting from too rapid depletion of electrolyte and water Local immediate and delayed irritative reactions occurred but were minimal

The authors concluded that thiomerin® administered by the subcutaneous route is an effective diuretic agent Absence of all but minor local irritative phenomena the apparent complete absence of systemic toxicity and the ease of administration provide definite advantage

Subcutaneous Administration of Mercaptomerin (Thiomerin®) Effective Mercurial Diuretic for Treatment of Congestive Heart Failure A mercurial diuretic which overcomes many of the objections inherent in the currently available preparations is known as mercaptomerin sodium (thiomerin® sodium) Not only is cardiac toxicity decreased but the amount of local irritation at site of injection is minimized to such a degree that the preparation is relatively painless on subcutaneous injection

Robert C Batterman David Unterman and Arthur C DeGraff[3] (New York City) studied the effectiveness and safety of mercaptomerin for treatment of congestive heart failure according to several plans First an effort was made to compare predictability of an effective diuretic response to intravenous or subcutaneous injection of the drug with that to an intravenous injection of mercurophylline For this purpose 45 hospitalized patients with varying degrees of congestive heart failure were given the diuretics when preliminary control periods indicated that sufficient time had elapsed to evaluate concomitant therapeutic measures From data on predictability of satisfactory diuresis that is a 3 lb weight loss mercaptomerin administered subcutaneously was decidedly satisfactory Predictability of response whether patients received mercurophylline intravenously mercaptomerin intravenously or the latter subcutaneously was identical Urinalyses after administration of the diuretic revealed no abnormality in any patient

(3) J A M A 140 1268 1 71 A g 0 1949

cumulation of edema fluid was estimated at about 8 kg Intravenous injection of 2 cc. mersalyl and theophylline solution caused urinary excretion of 17 Gm. chloride calculated as sodium chloride Three days later the same dose resulted in excretion of 6 1 Gm and urinary volume was progressively diminished ending finally in oliguria. A later injection of 4 cc mersalyl and theophylline solution did not affect urinary water or chlorides As the patient was ingesting only 1 Gm salt/day excretion of 23 1 Gm salt (395 m Eq) accompanied by only 2 2 kg water apparently depleted the extracellular electrolytes A week later she had retained 3 4 kg water which further hydrated and diluted the electrolytes She died of renal and cardiac insufficiency

Reversible features of the low salt syndrome either from spontaneous remission or therapy with salt suggest that it is a state of renal insufficiency dependent on low plasma levels of sodium and chloride The diuretic and nitrogen lowering action of hypertonic saline solution has sometimes been dramatic as in the following case

Man 67 with arteriosclerotic heart disease severe ascites and edema lost over 500 m Eq chloride in urine in 10 days as a result of mercurial and xanthine diuretics Characteristic symptoms and signs appeared and urinary output diminished. Transfusion of whole blood did not initiate diuresis nor did use of 5 per cent dextrose intravenously Probably the latter only served further to dilute the electrolytes But intravenous injection of 255 m Eq salt (16 Gm.) apparently restored electrolyte balance sufficiently to allow diuresis to begin In four days urinary output increased to well over 1 L however chloride output of urine remained exceedingly low and symptoms disappeared Although he had gained 2 9 kg in weight diuresis initiated by salt resulted in loss of this amount and a further loss of 1 kg

Of the 21 patients with the low salt syndrome 10 died and 11 recovered In most of the fatal cases terminal renal insufficiency was considered only in retrospect Injection of hypertonic sodium chloride solution was not accompanied with adverse symptoms when plasma electrolytes were low Venous pressure was measured simultaneously and usually there was no change Presence of pulmonary congestion did not contraindicate injection of hypertonic sodium chloride

The mechanism by which lowered electrolytes contribute to renal insufficiency is unknown Theoretically if adequate water is available and plasma is being filtered by glomeruli normal kidneys should be able to excrete water and retain salt until electrolyte balance is restored The abnormal (hypertensive cardiac or aged) kidney may be deficient in some

of were (1) drowsiness weakness and lethargy (often wrongly attributed to sedatives) (2) loss of appetite sometimes with thirst (3) nausea and occasional vomiting (4) occasionally abdominal and muscular cramps and (5) the secondary symptoms of an increase in extracellular fluids when edema was already present In every patient observed there was some degree of organic renal disease usually without renal insufficiency or a functional renal disturbance such as that associated with congestive failure

Therapy was aimed at rapid restoration of concentration of sodium and chloride in extracellular fluids to relatively normal levels by intravenous injection of hypertonic solution of sodium chloride (5 or 6 per cent) Since the problem in these patients was overhydration because extracellular fluid contained an amount of sodium chloride insufficient to maintain normal osmotic equilibrium the most rapid method of restoring concentrations of sodium and chloride to normal was to administer salt without water Experiments showed that intravenous administration of 5 or 6 per cent sodium chloride solution could be tolerated if given slowly the venous pressure rising only slightly if at all Although salt can be given orally the amount usually necessary to restore electrolyte equilibrium may be large (20-40 Gm) can produce gastrointestinal disturbances and may have an erratic rate of absorption The amount of sodium chloride given depended on calculation of the deficit in plasma in estimated interstitial fluids and in accumulated edema Normal extracellular fluid volume was considered 20 per cent of body weight Edema fluid if present was roughly estimated from gain in body weight Plasma levels of chloride and carbon dioxide combining power were followed daily subsequent injections of salt were based on these values Usually when plasma level of chloride reached 90 95 m Eq /L diuresis was well established As a rough approximation for a 70 kg man 17 1 m Eq sodium chloride (1 Gm) should be expected to elevate plasma levels 1 m Eq./L if edema is not present and salt is not excreted

Development of the low salt syndrome is illustrated by the following case

Woman 30 had subacute and chronic rheumatic endocarditis with involvement of mitral and tricuspid valve Extracellular ac

vania Hospital, 1937-47, Inclusive was made by Joseph B Vander Veer and P T Kuo[6] (Philadelphia) Of 26 628 pregnant women delivered during this period 409 had heart disease Types of heart disease were in approximately 80 per cent rheumatic in 12 per cent hypertensive cardiovascular in 4 per cent congenital Of the 409 patients 31.3 per cent were given digitalis at various periods before during and after pregnancy There were 14 maternal deaths (mortality rate of 3.4 per cent) among the 409 patients Heart failure was directly or indirectly responsible for 10 deaths Seven patients with rheumatic heart disease died between the seventh and eighth month of pregnancy and three died in the first 48 hours of puerperium Acute infections were the cause of death in 7 of the 14 patients precipitating acute congestive failure in 4 There were 54 fetal deaths (13.2 per cent) prematurity was the commonest cause Approximately 50 per cent of patients were delivered by use of low forceps during the second stage of labor Major operative procedures were rarely performed on patients with rheumatic heart disease unless there were gynecologic indications

Systolic murmurs of grade 1 intensity are of little significance during pregnancy especially if best heard in the pulmonic area If the patient gives a history suggestive of previous rheumatic infection and the murmur exceeds grade 1 in intensity a diagnosis of potential heart disease should be made Such murmurs can best be diagnosed after delivery however frequent examination of heart and lungs during pregnancy and labor should be made to determine the functional capacity of the patient Decompensation is most often manifested by elevation of respiratory rate tachycardia and appearance of moist rales at lung bases Pulse rates exceeding 110/minute and respiratory rates above 24/minute indicate onset of acute heart failure

With the possible exception of patients with coarctation of the aorta all patients functionally in class 1 and most in class 2 may be allowed to undertake pregnancy Patients functionally in classes 3 and 4 with or without a previous history of decompensation and those with auricular fibrillation should be advised against undertaking pregnancy If such patients are pregnant when first examined and have not passed the

(6) Am Hea t J 39.216 J ry 19 0

functions Whether the low salt syndrome occurs only with renal disease or renal functional disturbance cannot be stated at this time Return of renal function probably does not depend on restoration of circulatory efficiency through increases in blood volume for venous pressure was not reduced during anuria Nor does it depend on adequate levels of blood pressure The hazards of rigid restriction of sodium chloride in diets of cardiac patients used concomitantly with mercurial diuretics cannot be overemphasized

Use of Potassium Chloride and "Digoxin" in Congestive Heart Failure Because many cases of poisoning have resulted from the use of purified glycosides of digitalis in the treatment of heart disease and because damaged myocardiums are known to be deficient in potassium I E Buff[5] (Charleston W Va) tested the value of potassium therapy in patients with congestive heart failure The results were satisfactory Therefore 40 patients were treated with combined potasium and digoxin therapy (digoxin is a pure digitalis glycoside which is excreted with moderate rapidity)

Eighteen of the 40 patients had symptoms of digitalis poisoning when they were first seen They were given 5 10 Gm potassium chloride in milk orally or by intubation When the patient recovered from digitalis toxicity a maintenance dose of 1 0 Gm potassium chloride in milk was given three times daily for one week Then administration of the smallest dose of digoxin which would maintain digitalization was begun The remaining 22 patients were in failure but had not previously been digitalized They were given 0 5 mg digoxin and 1 0 Gm potassium chloride three times daily until a definite level of therapeutic digitalization was obtained After digitalization maintenance doses of digoxin and potassium chloride were established

The response of these patients to combined therapy was good Potassium seemed to enhance the action of digoxin and toxicity did *not occur Under other regimens especially* in older age groups mental depression and lack of co operation are noticeable but with this therapy patients were alert and co operative

***Cardiac* Disease in Pregnancy Study of Patients with Heart Disease at Philadelphia Lying In Division of Pennsyl**

(5) South M J 4 1037 1040 December 1949

colored cinematographs of the auricles of the intact dog s heart at speeds up to 2 000 frames/second Projected at 8 frames/second motion of the auricles was slowed 250 times A magnifying lens enlarged the auricle 100 or more times The auricular contraction wave was actually seen for the first time in this way Over 75 000 ft of film from experiments on over 200 dogs have been studied Arrhythmias were produced by aconitine and by postelectric stimulation methods A dual beam cathode ray oscillograph was used in some experiments and in others multiple channel electrocardiographic studies were used

It was concluded that all types of auricular arrhythmia (premature extrasystoles paroxysmal tachycardia flutter and fibrillation) arise from a single focus and that circus movement does not occur When a drop of 0 2 per cent solution of aconitine in benzene was placed on a small area of the wall of the auricle auricular fibrillation usually resulted after a few minutes When the ectopic focus was cooled by spraying with ethyl chloride the rhythm often changed in the following order from auricular fibrillation to flutter auricular tachycardia and sinus rhythm with auricular premature systoles When cooling was stopped and the point of application of aconitine was allowed to come toward body temperature a return of arrhythmias in reverse order was usually observed

Mechanism of Auricular Flutter and Fibrillation Topical administration of aconitine as a subepicardial injection of a dilute solution or an application of a few crystals on the epicardial surface of any part of the exposed auricle of a dog causes in a few minutes the appearance of a regular auricular tachycardia with rates of approximately 300 beats/minute Often the injection of aconitine causes an auricular fibrillation to appear David Scherf and Rosario Terranova[8] (New York Med College) continued their investigations of this phenomenon to accumulate further evidence that the aconitine tachycardia actually represents auricular flutter and not a tachycardia peculiar to the drug

Studies showed that auricular fibrillation could be transformed into auricular extrasystoles and flutter by slowing of the rate of stimulus formation with cooling the site of application of aconitine Cessation of the cooling led to reappearance

(8) Am J Phy 1 159 137 14 O t b 1949

fourth month of pregnancy abortion is indicated Thereafter conservative management is usually advisable Close observation adequate bed rest strict control of diet and sodium chloride intake and judicious use of digitalis usually maintain these patients in compensation through pregnancy and labor The earliest signs of heart failure are an indication for administration of digitalis Cesarean section and hysterotomy are usually not indicated in patients with rheumatic heart disease with failure but are frequently helpful in patients with hypertensive cardiovascular disease with pre eclampsia and eclampsia Lightening of the circulatory load during the last few weeks of pregnancy accounts for the relatively rare occurrence of acute cardiac failure in the last month of gestation In most patients with heart disease surgery is not recommended because the mortality rate has been demonstrated to be much higher when operative procedures are used

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ARRHYTHMIAS

Because of its lifesaving value in paroxysmal ventricular tachycardia quinidine is often considered the drug of choice for paroxysmal auricular tachycardia Actually digitalis intravenously in the form of lanatoside C is usually to be preferred Because treatment of the two conditions differs an electrocardiogram should always be taken when there is doubt as to which condition is present

Two of the following articles offer strong evidence against the validity of the classic hypothesis that the circus movement is the basic mechanism responsible for auricular flutter and auricular fibrillation —Ed

Mechanism of Auricular Arrhythmias Since the classic studies of Lewis on the nature of auricular arrhythmias little has been published on the subject He believed that auricular flutter is due to a regular circus movement in the auricles which sweeps around the openings of the venae cavae He attributed auricular fibrillation to a circus movement of the same general type but the impulse was thought to pursue a tortuous and redundant path Paroxysmal auricular tachycardia was attributed to a rapidly discharging ectopic focus in the auricle

For three years Myron Prinzmetal Eliot Corday Isidor C Brill Alvin L Sellers Robert W Oblath Walter A Flieg and H E Kruger[7] (Univ of California) have been taking

(7) Circulation 1 241 45 Feb y 1950

they were frequently accompanied by substernal pain sudden collapse shock dyspnea or syncope The immediate prognosis was good because in all but a few patients normal rhythm was resumed following appropriate therapy The ultimate prognosis was not good in those who had underlying coronary or valvular disease however a fair number of these were able to carry on a useful occupation for years In persons with no organic heart disease prognosis was generally excellent However even in this group sudden death may occur death during a paroxysm occurred in one patient who had a structurally normal heart at autopsy

The treatment of choice for paroxysmal ventricular tachycardia is quinidine therapy Oral administration was successful in 46 of 57 episodes In patients seriously ill intravenous administration was successful in 20 of 31 attacks In 13 patients magnesium sulfate given intravenously was occasionally of value in 2 potassium salts given orally were of no value in 1 intravenous administration of morphine was of no value

It is concluded that the intelligent use of quinidine is of great value in this condition and frequently saves the life of the patient

Supraventricular Paroxysmal Tachycardia in Infants and Children is discussed by Stanley Gibson[1] (Northwestern Univ) The cause of paroxysmal tachycardia in infancy is obscure It may occur at any period during infancy but is likely to arise during the first few weeks of life The symptoms include restlessness and irritability poor response to feedings frequent vomiting ashen gray color with the possible appearance of distinct cyanosis as the attack progresses The respiratory rate is alarmingly increased and may reach 150/minute Because of rapid breathing and chest noises cardiac auscultation may be difficult The rapid heart rate alone furnishes the clue to diagnosis the rate is regular practically always above 200/minute and may be in excess of 300 As the attack progresses the liver enlarges and edema of the lower extremities may occur Unless rapid heart action is interrupted by therapy the course may be steadily downhill with fatal termination In this respect paroxysmal tachycardia in infancy differs from that commonly seen in older children and adults in whom the attack eventually subsides even without

(1) M Cl N rth Am 34 217 222 J ry 1950

of flutter and when the rate of stimulus formation again increased fibrillation appeared

During auricular flutter stimulation of the vagus nerve and cooling of the site of aconitine application were used simultaneously The flutter was abolished by the cooling and when it reappeared the rate slowly increased without any change of the form of auricular waves The long distance between P waves could not be explained by presence of a circus mechanism Occasionally stimulation of the vagus nerve during auricular flutter caused long pauses between the auricular waves this also spoke against presence of a continuous circulating wave

At the beginning of the action of aconitine a sinus tachycardia appeared and was inhibited by stimulation of the vagus later auricular flutter suddenly appeared and its rate increased during stimulation of the vagi From this it is concluded that two different types of stimulus formation were being dealt with The hypothesis is advanced that during auricular flutter there is a constant stimulus and the response of the auricle to this stimulus depends only on the length of the refractory phase

Paroxysmal Ventricular Tachycardia Study of 107 Cases is reported by Charles A Armbrust Jr and Samuel A Levine[9] (Harvard Univ) Patients were aged 13 83 however most were 50 70 Diagnosis was often suspected by simple bedside examination but was confirmed by electrocardiographic studies Clinically an occasional case was overlooked because only one heart sound could be heard to each cardiac cycle and the rate was estimated to be only one half of its actual value

In 79 patients (74 per cent) the underlying cause of heart disease was coronary artery disease generally with recent or old myocardial infarction Nine patients had rheumatic heart disease 13 no heart disease and 6 miscellaneous conditions There were 27 patients who had recurrences of prolonged attacks over a course of months or years the duration varying from hours to 24 days Digitalis seemed to play a role in the precipitation of paroxysmal ventricular tachycardia in only a small number of patients

Although attacks of tachycardia were often symptomless

(9) Circulation 1 28-40 January 1950

they were frequently accompanied by substernal pain sudden collapse shock dyspnea or syncope The immediate prognosis was good because in all but a few patients normal rhythm was resumed following appropriate therapy The ultimate prognosis was not good in those who had underlying coronary or valvular disease however a fair number of these were able to carry on a useful occupation for years In persons with no organic heart disease prognosis was generally excellent However even in this group sudden death may occur death during a paroxysm occurred in one patient who had a structurally normal heart at autopsy

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(1) M Cl n N rth Am ca 34 217 22 Ja ry 1950

specific measures to break the abnormal rhythm Moreo measures usually employed in older patients such as mass or compression of the carotid sinus pressure on eyeballs duction of vomiting quinine quinidine pilocarpine or phy stigmine are rarely effective in infants However digitalis often effective Digitalis was used successfully in all but 2 12 patients

If symptoms are not alarming and there is no vomiti digitalis may be given by mouth 50 mg initially followed 25 mg at four hour intervals Normal rhythm is sometim established in 24 hours but two or three days of therapy m be necessary If symptoms and signs are more severe digita in similar or even larger doses may be given intramuscularl In two infants whose condition was so grave on admission th digitalis would probably not have acted with sufficient rapi ity to save life acetylcholine bromide intravenously produce a prompt response One infant required only 1 mg but total of 7 mg was necessary in the other

Paroxysmal tachycardia in childhood is less serious tha in infancy and may respond to a variety of therapeutic meas ures Digitalis and/or quinidine are usually successful whe simpler measures fail

Treatment of Paroxysmal Supraventricular Tachycardi with Lanatoside C J Gordon Barrow (Atlanta Ga) treatec 26 patients with paroxysmal supraventricular tachycardia which was refractory to vagus stimulation with lanatoside C intravenously Usually injection of an initial dose of 1 2 mg was done in 60 120 seconds If rhythm had not reverted to normal in 30 minutes 0 4 mg more was given in the vein In one case a third dose of 0 4 mg was necessary before the rhythm was controlled but in all other patients arrhythmia was stopped by 1 2 1 6 mg of drug Lanatoside C proved non toxic and relatively free from unpleasant side effects Parrow believes it is the drug of choice at present for treatment of the acute attack of paroxysmal supraventricular tachycardia

(2) A n I t M d 3 116 119 J y 1950

ELECTROCARDIOGRAPHY AND OTHER PROCEDURES

The idea that electrocardiograms are useful only in primary diseases of the heart is erroneous Actually the tracings may be of suggestive value in such diverse conditions as myxedema familial periodic paralysis and changes in the concentration of certain electrolytes It is also important to realize that emotional disturbances many drugs and the process of aging may produce electrocardiographic changes in the absence of clinically important heart disease It cannot be emphasized too strongly that opinions based on electrocardiograms alone without integration with the entire clinical picture are likely to lead to grave diagnostic errors

The electrokymograph although still in the developmental stage and largely a research tool is beginning to offer information of clinical value Angiocardiography is proving of increasing value in detection of the various types of congenital cardiac disease but is not without danger It is a simpler technic than cardiac catheterization The relative hazards of the two procedures and the comparative value of the information yielded by them are as yet uncertain —Ed

Electrocardiographic Observations during Cardiac Catheterization are reported by I Ralph Goldman S Gilbert Blount Jr Allan L Friedlich and R J Bing[3] Although over all mortality in cardiac catheterization reported from various laboratories is low (0 1 per cent) certain complications may arise during the procedure—primarily cardiac arrhythmias recognition of which is important

The authors made electrocardiographic observations throughout cardiac catheterization in 50 patients One or more types of cardiac arrhythmia developed in all but one patient Auricular premature systoles occurred in 60 per cent nodal premature systoles in 78 per cent supraventricular tachycardia of auricular or nodal origin in 28 per cent and auricular flutter in 6 per cent Ventricular premature systoles occurred in 86 per cent and short bursts of ventricular tachycardia in 78 per cent Ventricular flutter was seen in 6 per cent Ventricular fibrillation developed in one patient during cardiac catheterization with a fatal outcome Various degrees of auriculoventricular block occurred in 8 per cent of patients and transient right bundle branch block in 12 per cent

With one exception withdrawal of the catheter resulted in cessation of the serious arrhythmias encountered Therefore prompt recognition of appearance of an arrhythmia is of great importance This may best be accomplished by continuous

(3) B ll J hn Hopk Hosp 86 141 168 M h 1950

electrocardiographic observation during cardiac catheterization

Differentiation of Changes in Q T Interval in Hypocalcemia and Hypopotassemia A Carlton Ernstene and William L Proudfit[4] (Cleveland Clinic) describe electrocardiographic findings in a typical case of hypocalcemia and in five cases of hypopotassemia due to various causes

Earliest effect of a low serum potassium content consisted of rounding and broadening of T waves T waves generally but not always decreased in amplitude also Q T interval was frequently prolonged and whether or not this change occurred was determined entirely by the degree to which duration of T waves was increased RS T segments were not lengthened but were often slightly depressed Duration of QRS complexes was increased occasionally Prominent U waves commonly appeared in limb leads and lead CF_4 and by partial fusion with the descending limb of the T waves sometimes caused further apparent lengthening of Q T interval

In contrast to findings in hypopotassemia the electrocardiographic pattern of hypocalcemia was simple and consisted entirely of prolongation of the Q T interval due to lengthening of the RS T segment

Hyperpotassemia and Electrocardiographic Changes in Uremia J Wener and N K M de Leeuw (Montreal) made electrocardiograms and took specimens of blood for chemical analyses at repeated intervals of five patients with uremia In one patient the final ECG s were obtained at the instant of death and in two others ECG s and serum for potassium determinations were obtained within one hour before death

The earliest electrocardiographic abnormality noted was elevation of the T wave which was especially apparent in lead CF_4 Peaked T waves were not always increased abnormally and in some instances only a slight elevation occurred which if taken alone without a previous tracing for comparison was well within normal limits T wave changes became apparent at serum potassium concentrations of 23 7 28 8 mg per cent At concentrations of 28 8 mg per cent and above depression of the S T segment with diphasic or inverted T

(4) Am H rt J 38 60 72 A gu t 1949
(5) Ca ad M A J 61 406-412 Oct be 1949

waves was noted P waves disappeared at serum potassium levels of 33 2 mg per cent and above Widening of QRS complexes indicating intraventricular block was observed at serum potassium levels of 33 2 mg per cent and complete disintegration of the entire QRS complex terminating in cardiac arrest was noted in the terminal tracing in one patient at a serum potassium concentration of 34 9 mg per cent

Severe renal insufficiency as evidenced by high nonprotein nitrogen and creatinine values was present in all five patients However there was no correlation between degree of nonprotein nitrogen and creatinine retention in blood and serum potassium concentration There was close correlation between potassium retention and volume of urine excreted Elevations of serum potassium levels were noted only in the presence of persistent oliguria or almost complete anuria Hypochloremia was present in only one patient Serum sodium concentration determined in only one patient was slightly below normal Serum calcium concentration varied from 6 05 to 9 63 mg per cent none of the patients showed any symptoms or signs of tetany Neurologic disturbances such as paresthesia weakness or flaccid paralysis reported in some cases of hyperpotassemia were absent

Order of T Wave Changes in Exercise Electrocardiograms Urs Straumann[6] (Basel) used a method for measured exercise with the patient recumbent to eliminate clinostatic influences due to changes from the erect to the prone position Tests were made with an ergometer attached to the foot of the patient s bed and manipulated with the arms The friction generated by moving the hand grips warmed copper plates set between wooden blocks From the temperature difference specific heat and size of the copper plates the calories created by effort were measured and converted into kilograms The load of exercise was divided into four grades increasing from 120 to 1 200 or more kg

Results of the tests were tabulated in percentage deviation from the resting average in each case

Ten healthy subjects aged 22 28 were given tests and showed striking lowering of T waves after effort of grades 3 and 4 which lasted about 1½ minutes or less depending on the energy expended The initial rise in T waves observed by

(6) C d log 15 86 110 1949

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(4) Am Heart J 38 260 272 August 1949
(5) Canad. M A J 61 406-412 October 1949

cardiographic abnormalities which at least superficially resemble those produced by organic myocardial disease The commonest abnormalities are displacements of the S T segment from the isoelectric line and lowering or inversion of T waves Since it seemed that suggestion of emotional states to a person under hypnosis might result in similar abnormalities Leslie L Bennett and Norman E Scott[7] (Univ of California) experimented on five normal persons In all five tachycardia was produced In one when emotional states of anxiety and anger were suggested the ECG showed definite T wave abnormalities In this person the procedure was as follows

PROCEDURE —Hypnosis was induced While the person was going to sleep he was told that all bodily sensations would disappear Tachycardia was then produced by suggestion After tachycardia was establish d the person was told of it and that he could do nothing about it even if he wished Then he was told that his helplessness made him angry—angry to the extent that his anger encompassed both himself and the hypnotist Immediately thereafter he was reassured and given suggestions for relaxation and sleep Three standard leads were taken during the period of hypnotic sleep anxiety and anger and deeper leep Additional control ECG s were made when the person was not hypnotized

The ECG s made during hypnotic sleep did not differ significantly from the control ECG however the ECG made during a period when anxiety was suggested showed definite deviations The most important abnormalities were accelerated rate lowering of T_1 and lowering or disappearance of T_2 and T_3 These electrocardiographic changes occurred 2 3 minutes after suggestions of anxiety the tracing reverted to normal within 60 90 seconds after the person was reassured There was a striking similarity between these abnormalities and those due to organic heart disease

Results of this experiment indicate that a diagnosis of cardiac disease in a patient should not be made from an ECG alone without relating it to the whole clinical picture

Study of Electrocardiogram in Persons over 70 Changes in the electrocardiographic scheme of elderly persons have been described a number of times but there has been no agreement as to the frequency of abnormal records R J Mc Namara[8] (Charleston W Va) attempted to determine incidence of abnormal ECG s in elderly persons without cardiac

(7) Am P t. 4 189 190 Decemb 1949
(8) G t 4 1 0 160 M y J 1949

other investigators was not noted and Straumann believ this to be due to absence of clinostatic influences

The second group tested comprised 31 patients 3 of whc had electrocardiographic signs of myocardial damage Th reacted to grade 1 exercise with decided lowering secondari of T waves Of six patients with questionable cardiac disea two reacted normally the other four had definitely lowered waves after grade 1 exercise Twenty two patients gave i evidence of cardiac insufficiency but their histories suggest that the myocardium might be overstrained Two of them h a primary rise and three a secondary lowering of T wav which was more pronounced than in normal subjects Six p tients in this group showed primary lowering of T wave whereas 11 reacted normally

Healthy subjects had maximal secondary lowering of waves averaging 17 per cent after grade 1 40 per cent aft grade 2 and 3 and 53 per cent after grade 4 exercises A bri summary of three cases reported by Straumann gives an id of what happens to T waves (1) A cardiac patient had primary rise of T wave height 55 seconds after grade 1 effo but a secondary lowering of 20 per cent in 7 10 minute On grade 2 exertion there was a marked primary rise followe in three to five minutes by a secondary lowering of 40 per ce of resting T wave height (2) A hypertensive patient reacte to grade 1 exercise with a secondary lowering of 30 per cen (3) A patient with bronchopneumonia and negative finding on the ECG showed an insignificant primary lowering bu a rather high secondary lowering of T waves after grade exercise This was a borderline case

It is shown that exercise tests with constant observatio of T waves give information about the adaptability of th heart muscle to physical effort The time element is importa in T wave interpretation for in the first 15 seconds th changes are rapid and primary lowering may even off in 3 seconds

Straumann compares his results with those reported b others

Production of Electrocardiographic Abnormalities by Sug gestion under Hypnosis Case Report There has been increas ing recognition that anxiety states fear neurocirculator asthenia hyperventilation syndrome etc may cause tr

enlargement and hypertension Patients selected for study were presumably normal from a cardiac standpoint at all standards except electrocardiographic there were 78 men and 22 women aged 70 and over who were receiving no cardiac medication and who were without significant cardiorespiratory symptoms Auscultation revealed no diastolic murmurs and no systolic murmurs of more than faint or moderate intensity Blood pressure was 160/90 or under A teleroentgenogram showed heart size to be within normal limits No patient gave a history of substernal effort pain or of previous severe chest pain suggestive of coronary occlusion

Abnormal ECG s were found in 30 per cent The commonest abnormalities were premature contractions, T wave changes low voltage of QRS complex and intraventricular conduction defects Thirty one per cent had only minor changes of indefinite significance such as premature contractions low voltage or P wave irregularity and 39 per cent had a normal ECG Electrocardiographic abnormality became more frequent with increasing age in the second half of the eighth decade but essentially normal outnumbered abnormal ECG s in persons over 80 Incidence of abnormal ECG s was higher among men

Electrocardiogram in Familial Periodic Paralysis Familial periodic paralysis is a rare disease characterized by recurrent attacks of quadriplegia which usually occur at night and are associated with a low serum level of potassium Harold N Perelson and Richard S Cosby[9] (Los Angeles) report electrocardiographic findings in two cases of familial periodic paralysis and discuss their diagnostic value

Man 25 was hospitalized during an attack of familial periodic paralysis Electrocardiograms revealed a moderate degree of sagging of RS T segment in lead I and depression of RS T take-offs in leads II and III In lead CF_4 the RS T take off was depressed and there was pronounced sagging of the RS T segment Q T was 0 6 second which with heart rate of 75/minute indicated marked prolongation Serum potassium level on the day after hospitalization was 13 mg /100 cc On the second day after hospitalization tracings showed a return to normal the Q T interval measuring 0 4 at a rate of 60 beats/minute T wave was elevated and the base narrowed as compared with the previous tracing Determination of serum potassium level done on this day was 26 2 mg /100 cc.

In another attack six years later serum potassium level was 7 8

(9) Am Heart J 37 1126 1134 J 1949

mg and the ECG showed prolonged Q T interval grossly abnormal T waves and depression of RS T segments in all leads Potassium chloride 1 Gm intravenously and 1 Gm orally four times daily was given The following day serum potassium value was 17 2 mg and the ECG appeared normal

In another patient on whom ECG s were obtained during the terminal portion of an attack of familial periodic paralysis U waves were seen in leads I II and CF_4 and T waves were diphasic in lead III

Common to the small number of tracings so far reported in familial periodic paralysis are prolonged conduction times and changes associated with cardiac depolarization and re polarization Prolongation of the P R interval intraventricu lar block and PS T abnormalities occur but with no uni formity from patient to patient The findings which appear most characteristic of hypopotassemia are prolongation of Q T interval depression of RS T segment and low rounded T waves This combination in ECG s is rare

Difficulties in Electrocardiographic Diagnosis of Myo cardial Infarction are discussed by Louis Levy II and Albert L Hyman[1] (Louisiana State Univ) Changes in QRS com plexes indicating infarction are of primary importance in electrocardiographic confirmation of this condition T wave and RS T segment changes alone are not sufficient to indi cate presence of dead cardiac muscle T wave inversion alone may merely reflect a stage of ischemia and RS T segment changes alone may signify a state of injury however unless QRS changes appear and persist it is rarely justifiable to make an electrocardiographic interpretation of myocardial in farction Experimental production of myocardial infarction has demonstrated the stages through which cardiac muscle passes and the resultant electrocardiographic sequence of changes which correspond to the stages of ischemia injury and death of muscle The latter causes appearance of perma nent Q waves or QS waves over the area of infarction For Q waves to appear in leads taken over the area of infarction there must be living muscle in the ventricular wall opposite or adjoining the area of infarction since the normal sequence of activation in this area is responsible for genesis of the Q wave If the infarction involves only the outer portions of the

(1) Am H t J 39 243 62 F b y 1950

enlargement and hypertension Patients selected for study were presumably normal from a cardiac standpoint at all standards except electrocardiographic there were 78 men and 22 women aged 70 and over who were receiving no cardiac medication and who were without significant cardiorespiratory symptoms Auscultation revealed no diastolic murmurs and no systolic murmurs of more than faint or moderate intensity Blood pressure was 160/90 or under A teleroentgenogram showed heart size to be within normal limits No patient gave a history of substernal effort pain or of previous severe chest pain suggestive of coronary occlusion

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(9) Am Heart J 37 1126 1134 Jun 1949

standard electrocardiographic leads I II and III one of two points on the body is connected to each end of the galvanometric string or whatever recording device is used Therefore these leads are called bipolar Leads I II and III represent respectively the difference in potential between the right and left arms right arm and left leg and left arm and left leg *Since each standard lead represents the difference in potential between two points on the body* an ECG will not reveal with *certainty the nature and magnitude of the* electrical changes occurring at each of these points separately

In order to record electrical potentials of a single point on the body the electrode known as the central terminal T was created by connecting each of the three extremities used for the standard leads to a common point through a resistor of 5000 ohms The potential of this electrode undergoes no or only slight fluctuation during the cardiac cycle An ECG made by connecting this electrode through a galvanometer with some point on the body is therefore a record of the uncomplicated potential variations of a particular point In contrast to a standard lead the record is unipolar

Lead IV was then developed It is made by recording the difference in potential between a point on the thorax near *the* apex of the heart and another on the back close to the angle of the left scapula *In a sense this is an asymmetrical* bipolar or a relatively unipolar lead in which one electrode being close to the heart contributes potentials of considerably larger size than the more distant electrode In lead IV the problem of determining what is occurring electrically at each electrode is perhaps more difficult than with the standard leads because the electrodes are not equidistant from the source of the potential Furthermore the potential of the distant electrode is not indifferent and varies greatly between patients and from time to time in the same patient

It is now generally agreed that the central terminal T *is the closest to being a zero potential electrode* and with the introduction of a resistance of 500 ohms into each of the three branches the approach to a *zero potential is even* greater

In 1935 it was demonstrated that the Q wave of leads I II or III in myocardial infarction result because the left arm in lead I and the left leg in lead II were either partial or com

myocardium or is intramural a Q wave may not appear al though the QRS configuration is usually modified

Routine ECG s should include the three standard leads and at least precordial leads V_1 through V_6 In patients whose clinical history suggests infarction if these leads are not confirmatory additional exploration with other precordial leads should be undertaken Posterior lesions may show up well in ECG s taken at the ventricular level in the esophagus or in leads taken over the ensiform cartilage Although a large Q wave in lead V_F suggests the possibility of a posterior le sion presence or absence of such a wave can easily be deter mined from leads II and III Patients without cardiac disease may have a relatively large Q wave in leads III and V_F due to a horizontal clockwise rotated apex forward heart position High lateral lesions are best demonstrated in precordial leads taken over the anterolateral aspects of the third and fourth *left intercostal spaces Serial ECG s furnish valuable infor* mation Whereas changes in a single ECG may not confirm a diagnosis of infarction serial pictures demonstrating a pro gression of changes may be diagno tic

The ECG is still only a laboratory procedure which is an adjunct to confirmation of clinical diagnosis of myocardial infarction and should not be relied on completely to establish or disprove diagnosis of coronary occlusion Although in serial ECG s changes of infarction are highly characteristic their absence does not rule out diagnosis of myocardial in farction Too frequently diagnosis of myocardial infarction rests on T wave changes alone and conversely the absence of changes in ECG s is used as the only negative evidence in ruling out diagnosis of coronary occlusion in a patient whose history and other laboratory findings are diagnostic of infarc tion QRS changes should be present for interpretation by ECG of myocardial infarction however there may be in farction without QRS changes so that confirmation by ECG is impossible Although most patients with myocardial infarc tion have ECG s which confirm the diagnosis occasionally the ECG shows no characteristic changes in these patients

Unipolar Electrocardiography, Including Intracardiac Leads, in Diagnosis of Myocardial Disease is described by Charles E Kossmann[2] (New York Univ) In taking the

(2) B ll New York A ad Med 26 20 46 J n y 1950

tricular hypertrophy and right bundle branch block it is de layed in right precordial leads

As in the standard leads modifications in the precordial leads which occur in cases of ventricular infarction are (1) modifications of QRS (2) elevation or depression of S T seg *ment* (3) *change in* T wave Curves are either central or marginal The central curve is characterized by a QRS which is entirely negative and in clinical curves usually slurred or notched The marginal curve is characterized by a QRS which begins with an abnormally deep or broad Q wave followed by an R wave of variable size and occasionally a ter minal S wave The form of the S T segment and T wave with central and marginal curves depends on a variety of factors the most important being age of the infarct

In a considerable percentage of patients found at autopsy to have died from myocardial infarction electrocardiographic abnormalities were not diagnostic Despite newer leads con siderable caution must be exercised before a diagnosis of myo cardial infarction is made on the basis of ECG s alone

Esophageal leads are useful in the study of the electro physiologic behavior of the left atrium because the esophagus is normally in apposition to the posterior wall of this cham ber When the electrode is introduced through the nose it is usually at a level of 32 5-40 cm from the external nares Leads from the atrial region are characterized by a diphasic P wave Leads from the ventricular levels (45 50 cm from the external nares) are used for diagnostic purposes only sporadically be cause the desired information usually can be obtained more easily by leads from the surface of the body Catheterization of the heart has been used to study electrical potentials de veloped in the interior of the heart but it is not likely that this method will have any direct clinical application

Laboratory methods which may soon be of practical value clinically *are as follows* (1) *Plotting null potentials of* QRS on the chest by making ECG s from numerous points on the chest and abdomen and determining those in which the algebraic sum of the area of QRS deflection is zero These null potential points are then joined by a continuous line This method though at present unwieldy is useful in studying relative size and direction of Q R and S vectors (2) *In vectorcardiography QRS is regarded as a* vector which

plete semidirect leads from the region of infarction Later it was shown that the electrical position of the heart could be estimated from relationships between the extremity and pre cordial potentials There has been a tendency to regard the electrical and the anatomic positions of the heart as identical Furthermore it has been assumed that a specific form of QRS in an ECG of an extremity potential means that the extremity has a specific anatomic relationship to a ventricular chamber and/or its cavity It is probable that neither of these assump tions is always fully justified particularly in the abnormal heart

Extremity potentials are often inconveniently small how ever they may be made 50 per cent larger by simply breaking the connection between the central terminal and the extremity being studied

It is possible to approximate extremity potentials by plac ing one electrode on the extremity to be studied and the other on the body at a point as diametrically opposite as possible Curves thus obtained are approximately twice the size of those with the use of the central terminal and no special equipment is necessary

Precordial leads differ from extremity leads principally in that they are closer to the surface of the heart therefore the records more closely resemble direct leads from the sub jacent surface In a normal person the exploring electrode is moved from the right sternal edge (lead V_1) to the left ante-rior axillary line (lead V_6) Right precordial leads are char acterized by a small R deep S and T wave which may be in either direction but is usually upright in adults These leads *are assumed to be similar to those which would be* obtained if the electrode could be placed on the epicardial surface of the right ventricle Left precordial leads are usually character ized by a small Q and S and a prominent R with an upright T wave These leads are assumed to be similar to but smaller than those which would be obtained if the electrode could be placed on the epicardial surface of the underlying left ven tricle Maximal normal time usually given for the interval between beginning of QRS and peak of R wave in leads V_1 and V_2 is 0 03 second, and in leads V_5 and V_6 0 05 second In left ventricular hypertrophy and left bundle branch block the deflection is delayed in left precordial leads in h ven

tricular hypertrophy and right bundle branch block it is de layed in right precordial leads

As in the standard leads modifications in the precordial leads which occur in cases of ventricular infarction are (1) modifications of QRS (2) elevation or depression of S T seg ment (3) change in T wave Curves are either central or marginal The central curve is characterized by a QRS which is entirely negative and in clinical curves usually slurred or notched The marginal curve is characterized by a QRS which begins with an abnormally deep or broad Q wave followed by an R wave of variable size and occasionally a ter minal S wave The form of the S T segment and T wave with central and marginal curves depends on a variety of factors the most important being age of the infarct

In a considerable percentage of patients found at autopsy to have died from myocardial infarction electrocardiographic abnormalities were not diagnostic Despite newer leads con siderable caution must be exercised before a diagnosis of myo cardial infarction is made on the basis of ECG s alone

Esophageal leads are useful in the study of the electro physiologic behavior of the left atrium because the esophagus is normally in apposition to the posterior wall of this cham ber When the electrode is introduced through the nose it is usually at a level of 32 5 40 cm from the external nares Leads from the atrial region are characterized by a diphasic P wave Leads from the ventricular levels (45 50 cm from the external nares) are used for diagnostic purposes only sporadically be cause the desired information usually can be obtained more easily by leads from the surface of the body Catheterization of the heart has been used to study electrical potentials de veloped in the interior of the heart but it is not likely that this method will have any direct clinical application

Laboratory methods which may soon be of practical value clinically are as follows (1) Plotting null potentials of QRS on the chest by making ECG s from numerous points on the chest and abdomen and determining those in which the algebraic sum of the area of QRS deflection is zero These null potential points are then joined by a continuous line This method though at present unwieldy is useful in studying relative size and direction of Q R and S vectors (2) In vectorcardiography QRS is regarded as a vector which

changes in size and direction from moment to moment and in several planes during electrical excitation of the ventricles The tips of these vectors are joined by a line

Electrokymography of Heart and Great Vessels Principles and Application are discussed by Bert R Boone George F Ellinger and Frederick G Gillick[3] (Nat l Heart Inst Bethesda Md)

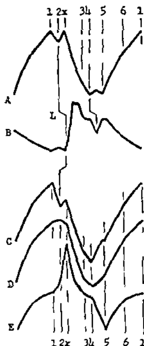
The electrokymograph is an instrument which records movements of the heart and great vessels It is based on the fact that variations occur in transmission of x rays through the heart and/or past its borders as the heart undergoes its phasic volumetric and positional changes It was specifically designed as an attachment for use with the roentgenoscope and electrocardiograph When these three units are utilized together in electrokymography the basic function of each is (1) the roentgenoscope provides the means for observing the cardiovascular silhouette and for positioning the electrokymographic pick up unit over a selected area (2) the electrokymograph converts motions and density changes of the selected points to corresponding current variations and (3) the electrocardiographic galvanometer records these variations on moving bromide paper resulting in an electrokymogram

The electrokymograms of 140 persons aged 17 32 who had no clinical evidence of cardiovascular disease were studied Although no standard positions for the patient or views have been established for routine electrokymographic examination of the heart the following segments of the cardiovascular silhouette are usually examined (1) posteroanterior projection (left ventricle pulmonary artery aortic knob and right atrium) (2) right anterior oblique projection (left ventricle pulmonary artery and dorsally the areas of the right and left atria) (3) left anterior oblique projection (left ventricle left atrium ascending aorta and right ventricle)

The electrokymograph is so connected to the galvanometer that a descending limb results from medial movement of a particular border decrease in density of a part or any combination of these changes which increases transmission of x rays An ascending limb results from lateral movement of a border increase in density or any combination of these changes which decreases transmission of x rays A method

(3) A I t Med 31 1030 1056 D mbe 1949

of standardizing amplitude has yet to be perfected The left and right ventricular electrokymograms have basically similar configurations Each cycle consists of a major descending limb essentially due to the medial movement of the ventricular border during systole and an ascending limb associated with lateral movement of the wall in diastole *Correlation with a simultaneously* recorded carotid sphygmogram helps to identify onset of ventricular ejection and of isometric relaxation respectively Two lag factors must be taken into account



F g 91—M thod f te p t g lect kym g m *A C D E* a t s f l ft t cul l ct okymog am n mal p s *B* otid phygmog m *L* cor ect n f t f f g f ca i d d g y t m a d p lse wa t m i V t l l d ph s f d e y f (Cou te y f Boo B R t *I* A l t M d 31 1030 1056 D mbe 1949)

when making the projection from the carotid pulse wave to electrokymogram (1) passage of the carotid pulse wave from the neck through the recording apparatus takes 0 01 second (2) passage of the pulse wave from the root of the aorta to the carotid artery takes (01 0 03 second

Figure 91 illustrates the commonest type of ventricular curve (*A*) with some normal variations (*C D E*) Using the carotid sphygmogram (*B*) interpretation can be made in terms of the physiologic phases of the cardiac cycle During the isometric contraction phase the ventricle is a closed chamber undergoing no volumetric change but is changing from an ellipsoid to a more globular shape producing a positional change of the border Direction of the movement depends on the point at which the record is taken It is usually a descending limb in the posteroanterior projection but may be ascending or horizontal Usually in the ejection phase (*2 3*) following the opening of the semilunar valves at 2 the ven

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device and a fluoroscope The photoelectric tube is activated by x rays falling on the fluorescent material and the resulting electric current is led to the electrocardiographic apparatus Variations in intensity of x rays are translated into variations in electric current and recorded as a line on photographic paper marked with lines indicating time intervals An increased flow of current due to increase in intensity of x rays reaching the fluorescent material causes the line being traced on the paper to be directed downward a decrease in current causes the line to be directed upward The pick up unit is mounted between the patient and the fluoroscopic screen and is positioned so that the center of its fluorescent surface is opposite the border of the heart When the heart border moves laterally intensity of the x rays reaching this surface is reduced and the line being traced moves upward To permit identification of the phases of the cardiac cycle on the electrokymogram the carotid pulse is simultaneously recorded on the same photographic paper using a pressure capsule fastened over the carotid artery on the patient s neck

The electrokymographic pattern of various parts of the normal heart shadow is established It is of value in detecting many pathologic conditions By measuring the time relation between onsets of major ascending limbs of the carotid pulse wave *and of the pulmonary artery* it was *found that* ejection from the two ventricles does not always occur simultaneously in the so called normal person and that the limits of asynchronous ejection in the normal is ±0 03 second Asynchronous ejection in excess of 0 03 second was almost always accompanied by electrocardiographic evidence of bundle branch block

Although several methods exist for determination of the various arrhythmias it is felt that additional information may be obtained on the mechanics of cardiac motion and thus indirectly the quality of myocardial contraction through study of the arrhythmias Paradoxical motion of an ischemic area of myocardium has been the subject of several articles Such electrokymographic abnormalities were found in patients with no definite electrocardiographic evidence to support a diagnosis of infarction or severe myocardial ischemia

Electrokymographic examination of four of the authors patients with radiologically and surgically proved constrictive pericarditis and calcification produced a constant type of ventricular curve with the appearance of a square wave i e its top is flat and it is practically devoid of secondary waves Similar waves were obtained from localized areas in three

tricular wall moves outward for approximately 0 02 0 03 second The protodiastolic phase (*3 4*) is the interval between the end of systolic ejection and closure of the semilunar valves During the period of isometric relaxation (*4 5*) the ventricles are again closed chambers and no volumetric change occurs Commonly the complex which follows aortic valve down at *4* resembles and is opposite in direction to that of isometric contraction The ventricle fills rapidly in early diastole producing a sharply ascending limb (*5 6*)

Each cycle of the electrokymogram taken from the areas of the atria usually consists of a basic pattern of two or three waves Because the atria are thin walled and relatively inactive chambers riding on vigorously active ventricles transmitted motions from the latter or from adjacent arteries may dominate the curve The effect of this and other physiologic factors may vary from patient to patient on the right and left atrium or on different segments of the same atrium Electrokymograms from the pulmonary artery ascending aorta and aortic knob closely resemble the carotid sphygmogram

The electrokymograph is being used to obtain records of heart density changes hilar shadow movements pulmonary vascular flow etc By placing the aperture of the instrument over the body of the ventricle a record is obtained which resembles the volumetric curve of the ventricle Such a density curve reflects changes occurring with variations in the amount of blood within the heart and alterations in the posteroanterior thickness of the heart muscle Arterial type records were obtained from the hilar shadows and the peripheral lung fields making it possible to study pulmonary circulation However it is impossible to state in what specific types of cardiovascular disease abnormal electrokymographic patterns occur and what clinical value the instrument will have

Clinical Application of Electrokymography The electrokymograph introduced in 1945 by Frederick G Gillick and William F Reynolds[4] (San Francisco) is described as a fluoroscopic microscope designed to detect and record variations in intensity of a small beam of x rays

APPARATUS —The instrument consists of a photoelectric tube with fluorescent material covering the photosensitive side (called the pick up unit) an electrocardiographic apparatus as a recording

(4) Cal fo n Med 70 407 41 May 1949

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(4) Cal fornia M d 70 407 412 May 1949

yond the point of narrowing Less frequently the site of co arctation is seen to be proximal to the origin of the left subclavian artery a condition loosely referred to as infantile coarctation

Diagnosis of patent ductus arteriosus is best made by physical examination and confirmed by cardiac catheterization Angiocardiography shows elevation and enlargement of the left pulmonary artery and often reveals aortic dilatation at the site of origin of the ductus However this dilatation was observed in two patients who had neither ductus arteriosus nor ligamentum arteriosum and is not invariably present in patients with patent ductus arteriosus

Differential diagnosis of tetralogy of Fallot and transposition of the great blood vessels Eisenmenger s syndrome and common truncus arteriosus may be facilitated by angiocardiography In tetralogy of Fallot a left anterior oblique film taken two seconds after beginning injection shows simultaneous opacification of aorta and pulmonary artery simultaneous opacification of a large right and a small left ventricle stenosis in the pulmonary conus or artery and usually a small poorly filled pulmonary arterial tree

Angiocardiography supplies a method for classifying the various causes of dilatation of the pulmonary artery A true lateral view not only reveals the dilatation but rules out presence of pulmonary stenosis a possible cause of dilatation of the pulmonary artery Angiocardiographic demonstration of radiopaque material passing through a septal defect was possible in only about 30 per cent of suspected cases A few notable and convincing exceptions to the contrary were observed but in general diagnosis of septal defect by cardiac catheterization is a far superior method With angiocardiography diagnosis of pulmonary veins draining into the right heart may be made on living patients for the first time surgical implantation of the anomalous vein in the left atrium has been suggested as corrective treatment

Angiocardiography is of value in differentiation of various types of aortic disease It was found that arteriosclerosis does not increase caliber of the aorta Hypertension increases aortic diameter to as much as 46 mm (normal maximum is 38 mm as measured in left anterior oblique) and syphilis causes even greater dilatation Hypertension causes an even

subjects with suspected constrictive pericarditis The roentgen kymograph has also been applied to differential diagnosis of abnormal shadows in the area of the cardiac silhouette The authors approached this problem by setting up a crude model simulating a vessel with an aneurysm and a heart with a spherical tumor adjacent to it Selected patients with known tumors or aneurysms were observed and results were consistent with the electrokymographic patterns found on experimental models

The electrokymograph has certain advantages over the roentgenkymograph Movements as recorded are amplified so that smaller movements are brought out and larger ones more easily studied A larger number of cycles can be recorded Areas to be studied can be selected fluoroscopically in their optimal projections The slit can be alined in the direction of the motion of the part Correlations in time of movements of various parts of an organ are more accurate There are on the other hand some disadvantages Measurement of true amplitude of movements is not yet possible with the electrokymograph The precise point along the border of the part at which movement is recorded is not shown as it is on the roentgenkymogram More co operation from the patient is required The procedure is more time consuming there must be in the fluoroscopic room a technician trained in use of the apparatus but this training can be quickly acquired The authors suggest that the electrokymograph be used much as the spot film is used in gastrointestinal work

Clinical Angiocardiography Critical Analysis of Indications and Findings Charles T Dotter and Israel Steinberg[5] (New York City) made angiocardiographic studies on over 1 000 patients without fatality during 11 years In adequately demonstrating the exact features of coarctation of the aorta angiocardiography is an indispensable preoperative preparation In the left anterior oblique projection the ascending aorta is usually seen to be dilated and to give rise to large brachiocephalic arteries Strikingly dilated internal mammary arteries are often seen paralleling the sternum The actual site of coarctation is usually seen as a narrowing slightly distal to the site of origin of the left subclavian artery Generally the descending aorta is dilated for a short distance just be

(5) Ann Int Med 30 1104 1125 June 1949

Five cases were reported and are briefly described here

CASE 1—Girl 11 had systolic murmur pulse of 84 blood pressure of 130/70 axis deviation to left and no other signs of malformation Diodrast® showed a patent ductus arteriosus Operation was not advised because of mildness of symptoms

CASE 2—Boy 10 had left axis deviation and cyanosis Diodrast® revealed tricuspid atresia interventricular communication and hypoplasia of the pulmonary artery Blalock Taussig procedure was advised

CASE 3—Boy 11 had cyanosis enlarged heart left axis deviation and tricuspid atresia Vessels were normally situated but small Operation was not advised

CASE 4—Girl 15 with cyanosis and dyspnea had tetralogy of Fallot Blalock Taussig operation was advised

CASE 5—Boy 17 had Eisenmenger complex and interventricular septal defect Operation was not recommended

Death Following Angiocardiography Charles T Dotter and Frederic S Jackson[7] conducted a survey by questionnaire of all centers in the United States Canada Great Britain and Sweden *using angiocardiography A total of* 6 824 examinations were reported with death following 26 none later than June 30 1949

Death in three patients was complicated by others factors Twenty one of the other 23 patients had congenital heart disease 17 of these were cyanotic and 5 extremely ill Seventeen deaths occurred in children under 8 all with congenital heart disease 14 of whom were cyanotic No deaths were recorded in persons with healthy hearts except one—a patient with renal arterial disease Three deaths occurred in mongols

The commonest form of death reported was sudden respiratory arrest immediately or shortly after injection of contrast substance Autopsy was done in all but one case but the cause of death was rarely found In about half the cases there was evidence to suggest that the respiratory system was susceptible to injury Pulmonary edema was reported several times

Available data do not indicate that the nature of contrast medium number of injections premedication or general anesthesia significantly influenced angiocardiographic mortality Over half the patients who died received full doses of contrast medium (over 1 cc /kg body weight for children and a total dose of 40 cc or more for adults) and almost all patients were examined in the horizontal position

(7) R d l gy 54 5 7 534 Ap 1 1950

dilatation whereas syphilis causes irregularity in the aortic lumen variations in aortic wall thickness and aneurysm In dissecting aneurysm the aortic lumen abruptly narrows and aortic walls thicken at the site of dissection Discrepancy be tween the size of cardiac chambers and cardiac silhouette in angiocardiography is significant in diagnosis of pericardial effusion Though usually not necessary for diagnosis angio cardiography of patients with pulmonary heart disease shows dilatation of the pulmonary artery and right ventricle and in constrictive pericarditis gross dilatation of the superior vena cava Localization of mediastinal masses also is facili tated by angiocardiography If vessels are stenosed malig nancy may be suspected

Angiocardiography in Congenital Cardiopathies Technic and Results in 74 Cases E Donzelot A M Emam Zade R Heim de Balsac J E Escalle and M Antoine[6] (Paris) emphasize the importance of knowledge of the anatomy and physiology of the normal heart and large vessels and correct interpretation of malformations found in treating congenital cardiopathies Opaque visualization is valuable but compli cated and not without danger and should be reserved for cases in which other methods fail to give the required information Its special value is in making a correct diagnosis in aiding in the decision for or against operation and in supplying the op erating surgeon with information concerning size and course of the implicated vessels

Of 329 patients with congenital heart disease from a blue baby center in Brussels 74 were selected for angiocardiog raphy *A total of 408 x rays were taken of which 35 were* failures 77 fair 187 good and 109 excellent

Technic—Children were hospitalized and tested for allergy renal function and circulation time During the test they were re cumbent and x rays were made in the anteroposterior projection In jection of 1 cc /kg body weight of 70 per cent diodrast® solution was made into the external jugular vein with a small trocar inserted without local anesthesia The trocar fitted to a tube with Y connec tion. One arm of the Y led to a container of salt solution with a drop dispenser the other arm to the syringe containing diodrast® X rays were taken before injection and after use of diodrast® at a rate of six exposures in five to six seconds Patients reactions were feelings of warmth Elimination of diodrast® amounted to 70 per cent at the first urination

(6) A ch d mal d oe 42 35 49 J y 1949

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(7) R d logy 54 527 534 Ap 1 1950

PERIPHERAL VASCULAR DISORDERS

New technics for study of this group of disorders continue to be developed and of them the isotopic method would seem to offer special promise for the future In most instances the simple clinical methods are adequate for arriving at an accurate diagnosis A number of new vaso dilator drugs are being used and definitive knowledge concerning their value as compared to each other and to such surgical procedures as sym pathectomy should soon be forthcoming —Ed

Certain Aspects of Nature and Treatment of Oligemic Shock *are discussed by Irvine H Page*[8] *(Cleveland Clinic)* One fact on which all investigators of shock are agreed is that shock represents all embracing dissolution Therefore its over all effects can probably best be measured by a quotient repre senting cardiac output and oxygen consumption as a measure of effective blood flow In Page s opinion Gesell has most nearly approached this concept with his nutrient flow He assumes that in shock transport of nutrient material and carrying away of waste are interfered with either by dilution of blood or by reduction of flow Since effective blood flow is seriously reduced for long periods it is not surprising that widespread damage occurs Whether the lack of one specific element such as oxygen is chiefly at fault or whether many substances are involved is not known For reasons such as these it is probably unwise to continue exclusive use of the terms anoxia or hypoxia to explain the cause of tissue changes Whatever the mechanism widespread tissue ischemia of suffi cient persistence results in shock Blood pressure may be ex cessively low but so long as no tissue ischemia occurs shock does not appear

It has taken possibly 30 years to recognize fully the im portance of oligemia as a cause of shock Of especial impor tance have been demonstrations that loss of plasma at site of injury often is sufficient to cause shock Most investigators would now agree that this is not the only factor in production of shock but is certainly of prime importance Another vital demonstration was that in shock cardiac output is low These facts with low blood pressure produce the picture of early shock Then begins the period of generalized dissolution in which so many chemical reaction paths are disturbed as to

(8) Am. H a t J 38 161 191 A gust, 1949

cause the investigator to become both baffled and frustrated

In an attempt to find a standard method for production of experimental oligemic shock Page has studied the shock procedure in 482 dogs in the past three years Despite stand ardized technics survival was so profoundly influenced by un known factors entirely beyond control that establishing a regularly reproducible standardized shock seems to be only statistically possible

The problem of vasoconstriction in shock viewed super ficially seems relatively simple But closer analysis reveals extraordinary complexity and despite much good work there is still no satisfying answer There seems to be little disagree ment that vessels of the limbs are constricted and there is little doubt that resistance to blood flow is increased in liver and spleen The only important area so far studied in which re sistance decreases rather than increases is the coronary circu lation *Vasodilatation appears to play a prominent part in de* crease in resistance in coronary flow Vasoconstriction in the kidney is of special interest since this organ receives almost one fourth of total cardiac output Renal blood flow decreases sharply after hemorrhage with a disproportionate decrease *in glomerular filtration Repeated prolonged hemorrhage de* creases ability of the kidneys to respond to transfusion by restoration of control blood flow and filtration rate Explana tion of this vasoconstriction so intense early and persistent seems to be partly humoral and partly nervous

As far as the mechanism of vasoconstriction is concerned there is no cogent evidence to suggest the primacy of failure of the vasomotor center At least three possibilities suggest themselves to explain why blood vessels constrict when blood volume is reduced physical factors active neurogenic con striction and active humoral contraction Presence of humoral factors has been established but function of this renal vaso pressor system renin reninsubstrate and angiotonin in shock is not clear Although it is inferred that the renin vasopressor system acts as a homeostatic mechanism there is no proof of *this There is still* another humoral vasoconstrictor possibility It has long been known that defibrinated blood or serum does not perfuse well through isolated organs because of the vaso constriction it causes In conjunction with others Page has isolated from serum a purified substance named serotonin

with vasoconstrictor activity more than twice that of an equal weight of epinephrine As yet nothing is known about the part if any played by serotonin in shock

Page has found no regular correlation between survival after shock procedure and a number of obvious environmental factors such as weight of the animal amount of blood required to lower blood pressure degree of hydration season initial hemoglobin or hematocrit value and initial blood pressure Since there is good evidence to suggest that as shock progresses efficiency of the myocardium becomes impaired effect of ouabain on survival was studied It did not alter survival but tetraethylammonium chloride which blocks ganglionic transmission in all autonomic ganglions increased survival significantly Increased survival appears related to the fact that in dogs with total sympathectomy blood pressure can be reduced to lower levels and for longer times without producing shock than can be done in normal dogs Difference in reaction can be correlated with peripheral blood flow

In treatment of shock all agree that blood volume must be restored to normal in as short a time as possible In the terminal phase every minute counts Among the reasons for giving blood by artery instead of by vein are the following Blood pressure is restored to normal levels within a few minutes and pressure is controllable Blood volume deficits are automatically corrected That amount of blood will be taken into the circulation which is required to fill it at a given arterial pressure When heart and respiration have failed blood given into an artery often brings about resuscitation The procedure is simple, the apparatus is mobile and nothing that is not ordinary hospital equipment need be used Given by artery little more than half the amount of blood required when blood is given by vein is needed to restore arterial pressure In emergencies it makes little difference what fluid is administered to keep the circulation going until the more suitable blood is available

Arterectomy in Treatment of Intractable Pain Following Recovery from Acute Arterial Occlusion N E Freeman F H Leeds and R E Gardner[9] (Univ of California) report 10 cases of acute occlusion of a major artery by thrombosis or embolism in which the extremity was viable but intract

(9) Am H t J 38 329 335 S pt mb 1949

able diffuse pain and distal hypoesthesia with a protopathic pain response subsequently developed. The pain was continuous and subject to severe spontaneous exacerbations This pain had been termed ischemic neuritis Some patients found relief in grasping the foot and gently rocking back and forth in bed dependency did not seem to help the pain Walking appeared to ease it but most patients stated that exercise was prevented by intermittent claudication All complained of numbness in the involved member The pain was relieved temporarily by lumbar sympathetic block The site of obstruction was visualized by arteriography All but one patient underwent operative removal of the thromboed segment After operation the severe spontaneous pain was relieved though other types of pain due to ischemia might persist Two patients died of acute coronary occlusion nine days and four months respectively after surgery neither had had recurrence of pain up to the time of death The patient in whom arterectomy was not done was treated with rest and vasodilators for two years there was no change in the character of the pain over this period.

None of the patients showed any objective improvement in peripheral blood flow although functional recovery in the postoperative period would suggest some improvement in the circulation Eight patients showed no increase in ability to walk but in two there was some improvement over a period of months The neurologic findings remained unchanged.

Arterectomy is a relatively minor procedure and can be done even in the poor risk patient All operations were performed under local anesthesia Usually only 2 3 cm of the thrombosed vessel was excised. The authors believe that the relief of pain is not the result of any improvement in circulation but rather is due to interruption of some nerve reflex from the region of the thrombosed artery

Radioactive Isotopes in Study of Peripheral Vascular Disease Further Studies on Circulation Index with Evaluation of Diagnostic and Therapeutic Value of Priscoline.* The condition of the peripheral vascular circulation can be estimated by radioactive isotopes A method using radioactive phosphorus (P^{32}) to test the status of the peripheral circulation has been described previously Data so obtained not only afford a survey of circulatory efficiency but can be helpful as a guide to prognosis and treatment The method is applicable

with vasoconstrictor activity more than twice that of an equal weight of epinephrine As yet nothing is known about the part if any played by serotonin in shock

Page has found no regular correlation between survival after shock procedure and a number of obvious environmental factors such as weight of the animal amount of blood required to lower blood pressure degree of hydration season initial hemoglobin or hematocrit value and initial blood pressure Since there is good evidence to suggest that as shock progresses efficiency of the myocardium becomes impaired effect of ouabain on survival was studied It did not alter survival but tetraethylammonium chloride which blocks ganglionic transmission in all autonomic ganglions increased survival significantly Increased survival appears related to the fact that in dogs with total sympathectomy blood pressure can be reduced to lower levels and for longer times without producing shock than can be done in normal dogs Difference in reaction can be correlated with peripheral blood flow

In treatment of shock all agree that blood volume must be restored to normal in as short a time as possible In the terminal phase every minute counts Among the reasons for giving blood by artery instead of by vein are the following Blood pressure is restored to normal levels within a few minutes and pressure is controllable Blood volume deficits are automatically corrected That amount of blood will be taken into the circulation which is required to fill it at a given arterial pressure When heart and respiration have failed blood given into an artery often brings about resuscitation The procedure is simple the apparatus is mobile and nothing that is not ordinary hospital equipment need be used Given by artery little more than half the amount of blood required when blood is given by vein is needed to restore arterial pressure In emergencies it makes little difference what fluid is administered to keep the circulation going until the more suitable blood is available

Arterectomy in Treatment of Intractable Pain Following Recovery from Acute Arterial Occlusion N E Freeman F H Leeds and R E Gardner[9] (Univ of California) report 10 cases of acute occlusion of a major artery by thrombosis or embolism in which the extremity was viable but intract

(9) Am. H t J 38 3 9 335 Septembe 1949

able diffuse pain and distal hypoesthesia with a protopathic pain response subsequently developed The pain was continuous and subject to severe spontaneous exacerbations This pain had been termed ischemic neuritis Some patients found relief in grasping the foot and gently rocking back and forth in bed dependency did not seem to help the pain Walking appeared to ease it but most patients stated that exercise was prevented by intermittent claudication All complained of numbness in the involved member The pain was relieved temporarily by lumbar sympathetic block The site of obstruction was visualized by arteriography All but one patient underwent operative removal of the thrombosed segment After operation the severe spontaneous pain was relieved though other types of pain due to ischemia might persist Two patients died of acute coronary occlusion nine days and four months respectively after surgery neither had had recurrence of pain up to the time of death The patient in whom arterectomy was not done was treated with rest and vasodilators for two years there was no change in the character of the pain over this period

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to investigation of new drugs designed to treat peripheral vascular disease Morris T Friedell Walter Indeck and Fenton Schaffner[1] (Chicago) report observations on the use of priscoline® whose effect occurs chiefly at the termination of sympathetic nerves in vascular smooth muscle

The circulatory index is determined by intravenous injection of 200 μc (P^{32}) as a phosphate ion and application of a thin walled beta counter to the sole Counts per minute determined with a scaling unit are plotted semilogarithmically with time as the logarithmic function Values ordinarily fall in a straight line the reciprocal of the slope of this line is designated the circulatory index The most useful part of study of the peripheral vascular circulation with isotopes is alteration of the circulatory index by one of the vasodilators

Four main types of responses of the circulatory index have been noted In group 1 the circulatory index is initially in the arteriosclerotic range (below 0 110) and rises to normal after therapy In group 2 it is low and falls to a lower level after treatment In group 3 the index seems to be subject to variation This group is therefore divided into subgroup 3a in which the initial index is above 0 110 and falls to the arteriosclerotic range after treatment and subgroup 3b in which initial index is above 0 110 but below the mean of the normal group and rises beyond the normal range after treatment In group 4 the index is above normal range and rises even higher after treatment

Classifications by these groups have been correlated with clinical findings in 82 patients Correlation of clinical (subjective and objective) response to a drug with the type of alteration obtained in the circulatory index revealed that groups 1 and 2 patients yield the best clinical responses Group 3a patients do better than group 3b treatment was ineffective for group 4 patients

Intravenous injections of priscoline® have been used in recent months to determine these groupings In addition oral medication with this drug over prolonged periods has been used for therapy of various peripheral vascular disorders Prognosis of the groups as determined with priscoline® coincides with that of groups determined by other vasodilating mechanisms The drug appears safe and only occasional un

(1) Arch Int Med 85 667 674 Ap 1 1950

pleasant side reactions were encountered Priscoline® is apparently more effective in conditions in which symptoms are due primarily to diminished blood supply It is less effective in severe associated causalgic states

Measurement of Regional Circulation by Local Clearance of Radioactive Sodium *Dynamics of the blood tissue exchange* of a diffusible inert substance has recently assumed significance as a basis for measurement of blood flow If the diffusible tracer substance instead of being administered in the general circulation is introduced into the tissue in question it is apparent that its clearance from the tissue will depend on and possibly be a measure of local tissue circulation Seymour S Kety (Univ of Pennsylvania) made a mathematical analysis of the clearance of such an injected substance

According to this analysis the tissue deposit of diffusible tracer (Na^{+}) should decrease along a single exponential curve which if plotted semilogarithmically should yield a straight line whose slope (clearance constant) is a quantitative measure of total ability of the local circulation to remove and to supply freely diffusible substances

For testing applicability of the theory the human gastrocnemius muscle was chosen In all cases in which nothing was done to alter circulation clearance followed a simple exponential curve indicating the validity of the theoretical derivation To test responses of the clearance constant to alterations in circulation *studies were done in which a control period* was followed by some procedure designed to speed or slow local circulation Application of a tight tourniquet above the knee was invariably and immediately followed by sharp reduction in clearance constant to practically zero Release of the tourniquet after 10 minutes was associated with a clearance more than twice normal undoubtedly a reflection of *reactive hyperemia Exercise of the gastrocnemius* for one minute caused a considerable increase in clearance rate

Kety suggests that the clearance constant represents a valid and convenient measure of local circulation in its broadest sense and is therefore a clinically useful determination

Differential Diagnosis of Peripheral Vascular Diseases is outlined by Walter Redisch[3] (New York City) In the scalenus

(2) Am H t J 38 321 328 S pt mbe 1949
(3) J M Soc N w J y 46 38-243 M y 1949

anticus syndrome x ray verifies or excludes cervical rib or related anomalies of the transverse process Enucleation of a cervical disk may produce pain resembling that of scalenus anticus syndrome but is not accompanied by vascular symp toms Post traumatic segmental arterial spasm starts sud denly and is relieved by nerve block or etamon® chloride Sudeck s atrophy is diagnosed by x ray Primary Raynaud disease starts in the upper extremities occurs predominantly in women and invariably leads to trophic changes Occupa tional peripheral vascular diseases in workers with pneumatic tools pianists and typists may show a secondary Raynaud phenomenon In erythromelalgia (Weir Mitchell s disease) extremities are warm and painful Distress and pain is brought about by heat and relieved by cold whereas the contrary as a rule is true for occlusive disorders

Periarteritis nodosa involves peripheral arteries in regular rosary like beading biopsy is valuable though diagnosis will usually be suggested by other features of the disease Pri mary acute arteritis is rare and is seen mostly in children Secondary arteritis is not so rare and may occur in all age groups Longlasting deep venous disease almost invariably leads to secondary arterial disease Pallor absence of pulsa tions and trophic changes suggest that the pro ess has ex tended from the vein to the artery Superficial thrombophle bitis in a varicose vein is easily palpated as a hard nodule or cord with or without surrounding inflammation Pain on pres sure may be present in neuritis to the same extent as in deep thrombophlebitis Homans sign however is absent in neu ritis and present in a high proportion of cases of deep throm bophlebitis Absence of diminished reflexes presence of edema peripheral arterial disease or cardiovascular disease cachexia and history of prolonged bed rest preceding opera tion or childbirth all favor deep venous disease Pulmonary embolism is of course a handicap in diagnosis

Arteriovenous fistulas must be differentiated from heman giomas and pulsating metastases In hemangioma as in arterio venous fistula there is a localized protruding convolute of dilated veins but in contrast to the fistula no thrill or bruit and a Nicoladoni Branham sign of bradycardia cannot be elicited Pulsating metastases are almost invariably pathogno monic of primary cancer of the thyroid Thrill and bruit are

frequently present A predilection site is over the hip bone the mass appearing under skin of the buttocks Lymphangiomas may occur alone or mixed with hemangioma They are benign but may be extensive and affect a whole arm Differentiation of telangiectasias of the skin is easy Simple arborizing and spider telangiectasias are frequent in liver cirrhosis and in women during pregnancy and are occasionally seen in healthy persons Harmless papular capillary telangiectasias are easily differentiated by means of their red and firm surface from the livid more flabby lesions of Rendu Osler disease (familial hemorrhagic telangiectasia) The former never bleed the latter are characterized by a tendency to profuse bleeding Harmless papular telangiectasias occur almost invariably after middle age Port wine lesions of capillary nevus flammeus the vascular birth mark are well known

Glomera are physiologic structures present in large numbers in fingers and toes and in smaller numbers elsewhere in the skin which aid the heat regulation of the body Occasionally one or several glomera may produce a new growth and become visible as a small nodule in the skin Their differentiation from small hemangiomas is easy because of the extreme painfulness of the glomus tumor Osler s nodes are not present in an otherwise healthy person and the hemangioma is not characterized by the purplish blue color of a glomus tumor

The obliterating endarteritides frequently are accompanied by such generalized signs and symptoms as hypertension in lead poisoning and eye lesions in ergot poisoning Syphilitic and tuberculous types of endarteritis usually exhibit some other manifestations of their respective etiologies Differentiation of thromboangiitis obliterans from obliterating arteriosclerosis may be difficult Manifestations of arteriosclerosis in other parts of the body and presence of diabetes suggest obliterating arteriosclerosis rather than Buerger s disease There may be a history of heavy tobacco smoking in both disorders this is invariably found in Buerger s disease Buerger s disease usually starts in the lower but frequently affects upper extremities Obliterating arteriosclerosis on the other hand is usually confined to lower extremities Angiography is valuable in differentiating Buerger s disease from obliterating arteriosclerosis the typical segmented interruption of arterial filling with enormous collateral circulation in the small vessels in the

former is an impressive contrast to the localized block with or without opening of new channels in the latter

Usually arterial thrombosis occurs in persons who have generalized peripheral vascular disease especially arteriosclerosis and is characterized by sudden onset pain and pallor with or without cyanosis In pure venous thrombosis signs of arterial occlusion disappear after five or six hours If they persist more than six hours and are not influenced by measures known to release arterial spasm then it must be assumed that there is an associated organic arterial lesion

Chilblains are spots of swollen slightly cyanotic erythema caused by cold injury of minute blood vessels they occur in children and young adults mostly female Chronic perniosis has logically the earmarks of chronic local disturbance in minute blood vessels Ulcerations are frequent but superficial Chronic perniosis is localized chiefly around the ankles the predilection site for varicose ulcers is the shin Frostbite and trench (immersion) foot are thrombotic diseases of arterioles venules small arteries and sometimes small veins

Diagnosis of Portal Vein Obstruction Studies of Intestinal Absorption of Glucose Using Abdominal Collateral Veins In portal venous obstruction the collateral circulation carries part or all of the blood ordinarily consigned to the portal vein The collateral veins therefore may be expected to transport the products of intestinal absorption circuitously around the obstruction F Tremaine Billings Jr and Harold E DePree[4] (Nashville Tenn) attempted to determine whether the products of intestinal absorption could be demonstrated in the collateral veins of the abdominal wall in patients with portal vein obstruction and if so whether such a procedure might not assist in differential diagnosis of the etiology of ascites The oral glucose tolerance test was used Blood was drawn at regular intervals after ingestion of glucose simultaneously from the antecubital vein and from a vein in the abdominal wall and the blood sugar content was measured Sixteen patients with ascites were studied and 2 without ascites were controls

With hypertension of the portal vein higher levels of sugar were often demonstrated in blood from the veins of the abdominal wall than in blood from the antecubital vein The

(4) B ll J h H sk H p 85 183 199 Sept mber 1949

authors suggest that this procedure is helpful in determining whether or not there is portal vein obstruction

Arterial Air Embolism is discussed by Thomas M Durant M J Oppenheimer M R Webster and Joan Long[5] (Temple Univ) Air embolism may be classified into two types depending on site of entrance of air into the body In the first type air enters a systemic vein and tends if present in sufficient quantity to cause obstruction of the right ventricular outflow Up to 100 150 cc or more of air may be necessary to produce death This type has been called pulmonary air embolism since the pulmonary circulation is involved Air which enters the pulmonary veins produces an entirely different clinical picture and causes arterial air embolism The serious manifestations produced are dependent on obstruction of systemic arteries especially of the central nervous system and coronary vessels

It was formerly believed that air responsible for arterial air embolism either was injected from a pneumothorax apparatus or in the case of thoracic surgery was aspirated into open pulmonary veins However embolisms have occurred frequently in pneumothorax work when no air has been injected Others have occurred which complicated the tapping of pleural effusions for which no extrinsic air source could be implicated It is now known that air already present in the thoracic cavity can be an important source of embolisms if the therapeutic procedure provides access of air to the venous system and the pressure gradient from source to vein is sufficient Sources of air in arterial air embolism may be classified as intrinsic air in alveoli pulmonary cavities or pleural cavity extrinsic air either injected aspirated from tubing of pneumothorax apparatus or aspirated into pulmonary veins during open chest procedures In pneumothorax work injected air may reach a pulmonary vein directly but air may also reach such a vein indirectly if pressure in the pneumothorax cavity is raised sufficiently to tear an adhesion with production of a pleurovenous fistula Air from intrinsic sources cannot reach pulmonary veins unless trauma of the thoracic procedure produces an opening from source to vein There must also be a sufficient pressure gradient from source to vein and some factor to maintain patency of the opening

(5) Am H t J 38 481 500 O t b 1949

The *necessity for such a chain of circumstances* explains the rarity of accidents when needles are introduced into normal lung tissue After air from either an extrinsic or an intrinsic source has entered the pulmonary vein it is carried to the left heart and into the aorta From this point its route is determined to a considerable extent by the patient s position Air buoyancy tends to cause the gas to enter those branches of the aorta which are superiorly oriented with relation to the trunk of the vessel When air has reached the terminal arterial *branches of an organ the effects produced are the result* not only of the mechanical obstruction of the smaller vessels but of a neurovascular mechanism producing vasoconstriction

Clinical manifestations of arterial air embolism are somewhat varied They may be of sudden onset or there may be warning symptoms such as dizziness or faintness just before severe features become manifest After the warning symptoms there is usually loss of consciousness of variable duration Convulsions occur in less than half the cases After re*turn of consciousness various localized neurologic signs* may be noted These may disappear within a few hours or may persist for months Generalized cyanosis is noted in most instances and respiratory disturbances most often slowing of the respiratory rate are usually present Manifestations of peripheral vascular collapse are frequent These clinical features are nonspecific but there are five features which may be regarded as pathognomonic (1) detection of air in retinal vessels by ophthalmoscopic examination (2) Liebermeister s sign—occurrence of sharply defined areas of pallor in the tongue (3) marbling of skin (4) air bleeding—presence of air bubbles in blood escaping from a small skin incision in the most superior portion of the body and (5) x ray evidence of air in cerebral vessels The diagnostic value of these features is so great that they should be searched for in every case in which there is a possibility of arterial air embolism

The frequent involvement of the coronary arteries in arterial air embolism has been demonstrated by experimental and postmortem studies and it has been stated that obstruction of coronary arteries must be considered important in all cases of air embolism originating in the pulmonary circulation However there is a lack of data on whether air introduced experimentally into the coronary circulation can pro

duce ischemic areas in the myocardium or electrocardiographic changes of infarction The authors therefore carried out 18 experiments using 16 dogs In 14 experiments air was injected into the anterior descending branch of the left coronary artery and in 4 into either the left auricle or the pulmonary vein

On the basis of results it can be stated that air is not well tolerated within the dog s coronary circulation because six animals died and ischemic areas were induced within the myo cardium in all dogs Electrocardiographic changes were iden tical with those observed in instances of ischemia induced by other means The effects of vascular obstruction may be tran sient the air being rapidly disposed of but in some instances they may be sufficiently prolonged to result in persistent ischemia of the myocardium even after air bubbles can no longer be detected with the lumen of the vessel involved

The importance of the principle of air buoyancy was dem onstrated in these experiments in that air filled the superiorly located portions of the coronary circulation The importance of the application of this principle by use of the head down position in prevention of cerebral air embolism has been dem onstrated by others It seems logical to assume that the same principle could be applied effectively to prevention of coro nary involvement Since in man the right coronary artery arises anteriorly from the right aortic sinus and the left coro nary artery arises mesially from the left posterior aortic inus it should be possible to prevent air from entering these vessels by placing the patient in a position midway between left lat eral and prone There is indication that the initial dose of air may not be the only one since a fistula between the pulmonary vein and a pneumothorax or other air containing cavity may be opened and closed repeatedly Hence if there are warning symptoms of air embolism and the initial dose is not fatal it would appear logical to place the patient immediately in the favorable position described so that any subsequent emboliza tion may not have serious effects To prevent cerebral embo lism the patient should also be placed with head down It would seem wise to maintain such a position for several hours to allow the fistulous tract to heal

Pathophysiology and Treatment of Lower Leg Stasis Syn drome are outlined by Gunnar Bauer[6] (Genl Hosp Marie

(6) A g logy 1 1 8 F bru ry 1950

stad Sweden) At this hospital division and resection of the popliteal vein has for some years been the main therapeutic procedure in all patients with a lower leg syndrome of chronic edema induration ulceration and pain

Man s erect position is known to cause a certain amount of venous overloading in the lower parts of the leg In healthy persons this superfluous blood is easily removed by contractions of the calf muscles which act as a peripheral heart This mechanism demands normal functioning of the valves in the femoral and popliteal veins In patients with lower leg edema induration ulceration and bursting pain it has been demonstrated that these large veins are incompetent their valves having been destroyed by thrombosis or by phlebosclerotic processes In such cases superfluous blood cannot be effectively removed by contraction of calf muscles every relaxation of these muscles being immediately followed by a back flow of blood down the valveless main trunk This results in permanent venous stasis eventually followed by pain and tissue changes

A remedy for this condition is blocking of the main trunk in the popliteal region After this operation the calf muscle contractions drive the blood through numerous fine calibered channels into the muscle veins of the thigh and no backflow occurs Considerable experience with phlebography demonstrated the extraordinary ease with which collateral venous channels form the instant main trunks are blocked Study of the lower extremity in the vertical position after popliteal blocking showed that after a few calf muscle contractions the deep vein trunks were nearly empty and all blood was being driven through numerous channels past the level of the knee up into a rich network of mainly muscle veins in the thigh Once in the thigh blood was amply taken care of by the lively circulation in the powerful muscle masses in that part of the leg

Popliteal vein division has been performed 194 times at the Mariestad hospital The operation was apparently entirely risk free and immediate results were good Though the observation period is too short to allow final evaluation of late results follow up examination of 80 patients after 1 2½ years is encouraging

Nonsurgical Treatment of Peripheral Vascular Disorders is discussed by Walter Redisch[7] (New York City) General therapy of peripheral vascular disorders is concerned first with prevention of circulatory insufficiency second with promotion of increase of circulation and third with maintenance of compensation of insufficient circulation if compensation is achieved Requiring management of chronic arterial insufficiency are all patients with signs of peripheral arterial insufficiency or presenting evidence sufficient to suggest that they may be threatened by this disorder in the future The peripheral vascular routine includes prohibition of tobacco and food or drink containing rye grains prescription of 2 or 3 oz Scotch or Bourbon whiskey daily or 3 glasses of wine a foot care program scrupulous care to avoid injuries to extremities avoidance of exposure to cold and therapeutic appliance of postural changes This routine is the baseline for any additional active special treatment Management of chronic venous insufficiency on the other hand is aimed at facilitating venous deflux Sleeping with the foot of the bed elevated wearing of elastic bandages or stockings and walking exercises with these stockings in place is the basis

Papaverine hydrochloride about 0 05 Gm by intra arterial injection effects release of arterial spasm This heroic treatment has its place in acute arterial occlusion of all kinds including pulmonary embolism Oral doses of 50 100 mg three times daily are justified in vasospastic disorders and definitely beneficial in so called vascular crises Theobromine derivatives including aminophylline are worthless Nitroglycerin seems to be effective in the visceral circulation only Effects of histamine are probably confined to the skin Ether intravenously is an effective vasodilator but the danger of hemorrhage is too great Results with acetylmethylcholine chloride are not impressive and effects of intravenous use of typhoid vaccine are transient and do not justify use of so incapacitating a method in spastic disorders Priscoline* an imidazolene derivative has some usefulness in Buerger s disease (50 mg three times daily) There is no question about the beneficial effects of intravenous use of procaine on arterial spasm The most powerful and reliable vasodilators however are the different alcohols *The simplest and one of the most efficient*

(7) J Med Soc New Jersey 46 368 375 August 1949

is still ethyl alcohol in the form of good whiskey or brandy Nicotinic acid produces vasodilatation only in cutaneous vessels Niacinamide does not cause vasodilatation Nicotinic alcohol seems to hold good promise as a vasodilator

Treatment of primary Raynaud s disease is surgical Secondary Raynaud s phenomenon calls for treatment of any underlying vascular disease and usually treatment of the underlying psychoneurosis Wier Mitchell s disease (erythromelalgia) is one of the conditions in which for unknown reasons salicylates are almost a specific for pain In obliterating endarteritis in addition to rigid vascular routine therapy depends on etiology Treatment of Buerger s disease is predominantly based on the vascular routine as is treatment of obliterating arteriosclerosis Dietary treatment of arteriosclerosis is important and diet should always be low in fat and cholesterol

Management of acute arterial occlusion consists of intravenous or intra arterial use of papaverine intravenous use of procaine or diethylaminoethanol keeping the limb warm and watching for results for three to six hours If preliminary results are favorable vasodilators are continued if unfavorable paravertebral nerve block is done Whenever the patient s state permits Redisch proceeds with sympathectomy if nerve block gives a favorable result Treatment of arterial occlusion with anticoagulants is still experimental If the cause of the occlusion is an embolus in an otherwise not diseased blood vessel embolectomy should be performed Thrombectomy with resection of the diseased part of the blood vessel has no indication

In acute thrombophlebitis and prevention of thromboembolism in addition to elevation and rest there are but three basic approaches use of anticoagulants surgical ligation of efferent veins and the combination of both When thrombophlebitis is diagnosed before pulmonary embolism it seems unnecessary to proceed with venous ligation unless anticoagulant therapy is contraindicated It is contraindicated in all conditions in which there is an abnormal tendency to bleeding In these patients early ligation of veins on both sides is the procedure of choice Patients with early diagnosis of non extensive thrombophlebitis in whom no contraindication to anticoagulant therapy exists must be treated with this method

Chemical Sympathectomy H A Haxton[8] (Manchester) reports his experiences with phenol injection of the lumbar sympathetic ganglion in patients with various conditions

TECHNIC.—Two 12 cm needles are inserted through skin wheals 7 cm from the midline and opposite the second and third lumbar vertebrae. The needle must establish contact with the side of the vertebral body and by manipulation it is persuaded to slide tangential to the bone for a further distance of 1 2 cm. The point may be felt to pierce the psoas fascia and when it is in the correct plane a tentative injection of procaine should flow easily A careful watch must be kept for the welling of blood or cerebrospinal fluid from the needle Preliminary injection of 2 ml of 4 per cent procaine is made As a rule the patient notices warmth in the limb before it is detected by the observer but the sole of the foot should begin to warm up a few minutes after injection unless there is severe organic arterial obstruction Provided there are no symptoms of numbness or paralysis the injection is completed with a total of 10 12 ml of 10 per cent phenol in water The patient remains in the lateral position 15 minutes to prevent spread of the injection and can then get up and go home if ambulant.

In over 90 per cent of cases a warm dry foot resulted and in 60 per cent the foot remained warm and dry for months For some patients in whom the effect did not persist the injection was repeated and a good and lasting result obtained The longest follow up was nearly two years and the signs of sympathetic denervation remain Complications were few and consisted mainly of some irritation of the genitofemoral nerve which developed in about 10 per cent of patients causing hyperesthesia in the groin In one patient a low spinal analgesia lasted three hours and weakness of the quadriceps on the injected side lasted three months it was thought that the needle was incorrectly placed and the injection must have entered an intervertebral foramen

Uniform success was achieved by chemical sympathetic injection in six patients with intractable pain in amputation stumps In another patient with hyperhidrosis of the feet there was immediate and dramatic cure which remained complete Six patients with cold blue legs painful nodules of fat necrosis and in some chronic ulceration were treated with lasting benefit in all but one Similar relief was provided in two patients with severe chilblains In 65 patients with arteriosclerotic legs profound and lasting relief from rest pain was achieved in half and considerable relief in nearly all the re

(8) B M J 1 10 6 10 7 J 11 1949

mainder Pain due to inflammation near a gangrenous or in fected part was not however relieved by this treatment or by sympathectomy Phenol injections greatly improved the pre carious circulation in the foot and in several patients with gangrene of one toe healing was achieved with loss of only the affected digit Patches of gangrene on the heel and chronic ulcers on the outside of the leg have likewise healed with preservation of the limb The majority of 23 patients treated for intermittent claudication stated that they were benefited some considerably Of 58 patients with old white leg and similar deep venous thrombosis treated by phenol injection all but a few were benefited Explanation of this improvement lies partly in the removal of venous spasm with a resulting fall in venous pressure and partly in the improved nutrition of the capillary walls with reduced transudation into the tissues

Experiences with Tetraethylammonium Bromide, an auto nomic blocking agent are described by Gunnar Biorck and Borje Ejrup[9] (Stockholm) The effect of intravenous and in tramuscular injections of a solution of the compound were studied by means of blood pressure recording electrocardio grams oscillograms (at rest and after exercise) skin tem perature determinations electrocardiographic hypoxemia tests and determination of oxygen consumption

Results revealed that intravenous injection of tetraethyl ammonium bromide in man is followed by an immediate short lasting fall in blood pressure and in increased heart rate The effects were greater in hypertensive patients than in normal persons rate of injection and dosage were important In rab bits effect of intravenous injections of tetraethylammonium bromide on blood pressure was depressor whereas in cats it was depressor only with small and moderate doses and pres sor with larger doses In all instances heart rate was slowed These findings can be attributed to blocking of transmission of tonic impulses in the autonomic nervous system

Injection of tetraethylammonium bromide was almost im mediately followed by increased skin temperature both in nor mal persons and though to a lesser extent in patients with occlusive changes in arteries This increased skin temperature was independent of the fall in blood pressure Although oxy

(9) Acta m d Sca d 133 299 320 1949

gen consumption generally increased during injection no certain increase in oxygen consumption was found during the period of maximal rise in skin temperature No definite improvement of the electrocardiogram after induced anoxemia in cases with coronary insufficiency (the hypoxemia test) was observed neither shortly after injection nor after a series of therapeutic injections

Oscillograms on patients with occlusive changes in arteries given tetraethylammonium bromide did not demonstrate any improvement immediately after injection although the patients were subjectively improved Fifteen of 20 patients with occlusive changes in arteries showed after a series of 20 injections of tetraethylammonium bromide both subjective and objective improvement as measured by amount of exercise performed and by more rapid oscillographic recovery period Effect depended on completeness of the block In many large persons 5 ml of the drug was insufficient for production of complete block The larger doses (8 or 10 ml) required proved safe when given slowly The authors recommend a dose of 0 10 Gm/kg body weight There were few complications to administration of tetraethylammonium bromide The drug is not recommended for use in patients with complete heart block as lack of a cardiac mechanism compensating for the sudden drop in blood pressure may cause cerebral anemia and shock

Etiology of Gravitational Ulcers of Leg The term gravitational ulcer refers to chronic ulcers which occur on the lower half of the leg from chronic venous stasis of the lower limb Such ulcers are associated with one or more of the following signs of chronic impairment of venous drainage edema cyanosis induration sclerosis pigmentation loss of hair eczema and varicose veins of the affected limb Although these ulcers have long been thought to be due to varicose veins clinical observation and careful dissection have shown that many are due to obstruction of deep or superficial trunk veins

S T Anning[1] (Univ of Leeds) investigated the cause of ulceration in 270 patients by clinical examination and in a few cases by phlebography There was 192 women and 78 men in this series

In 88 6 per cent venous stasis was due to previous throm

(1) B t M J 2 458 464 A g 27 1949

bosis of deep veins in the leg Thrombosis followed pregnancy in 69 women the first ulcers occurring 3 months to 27 years after a postpartum white leg Antepartum thrombosis though less common than postpartum phlebitis is well recognized as a complication of pregnancy Fifteen patients gave a history of sudden pain and swelling of one or both legs during pregnancy Edema of the affected legs persisted and some patients developed varicose veins for the first time Thrombosis of the deep veins of the leg had probably occurred

Injury to one or both legs without fracture occurred in 60 patients Of those in whom there was no evidence of chronic venous insufficiency before injury 23 gave a history of swelling of the leg and 10 developed varicose veins after injury thrombosis from the injury was the probable cause Injury to the leg with fracture occurred in 11 patients Both direct injury to a vein and immobilization of the limb may have been factors in causing the thrombosis which followed Ulceration occurred 1 month to 26 years after fracture

In 6 patients thrombosis followed operation on a leg in 15 ulceration followed an infection of the leg and in 12 a period of recumbency or inactivity Twelve patients gave a history of phlebitis shortly after an operation Treatment of varicose veins appeared to be the cause of ulceration in 15 patients Injection of varicose veins seemed to intensify chronic venous insufficiency if already present and to produce it if not Thrombosis from miscellaneous causes occurred in 8 patients and from no apparent cause in 19 Of 31 patients with no history of thrombosis venous stasis and ulceration might have been due to varicose veins in 29 Of the 29 24 were women of whom 17 were parous The author concludes that varicose veins may be present as a result of thrombosis but primary varicose veins rarely cause venous stasis and gravitational ulcer It is stressed that concentration on treatment of superficial varicose veins is futile

Effects of Cortisone and ACTH on Periarteritis Nodosa and Cranial Arteritis Preliminary Report. Richard M Shick Archie H Baggenstoss and Howard F Polley administered cortisone to three patients with periarteritis nodosa and two with cranial arteritis and ACTH to two other patients with periarteritis nodosa Diagnoses were confirmed by biopsy

(2) Proc Staff Meet. Mayo Cl 25 135 M 15 1950

Treatment was continuous or intermittent for 3 weeks to 4½ months Dosage schedules varied

All seven patients had prompt subjective relief Fever subsided in 24-72 hours and sedimentation rates decreased gradually to normal Partial relapses occurred in five patients after withdrawal of the hormones but improvement followed resumption of treatment Despite initial improvement two patients with periarteritis nodosa died in cardiac and renal failure Autopsy showed complete healing of all arterial lesions However in the process of healing fibrous obliteration of the lumens of the vessels had occurred resulting in widespread visceral infarction Some evidence of hypercortisonism developed in most patients during treatment

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ANTICOAGULANTS AND THROMBOEMBOLIC DISEASE

The studies of several years ago established the value of anticoagulants in preventing thromboembolic complications following myocardial infarction Recent studies sugge t that th rout ne use of dicumarol® is also indicated in patients with congestive fa lure Thus far there have been only a few reports dealing with the long term prophylactic administration of dicumarol® to patients in whom further thromboembolic epi odes are apt to occur These preliminary reports are encouraging but the procedure should be regarded as till in the exp rimental stage There is evidence that certain drug uch as salicylates and sulfonam des enhance or prolong the action of dicumarol® The practical importance of this in relation to long term therapy is obv ous —Ed

Dicumarol® Prophylaxis of Thromboembolic Disease in Congestive Heart Failure Thromboembolic disease formerly considered largely a postoperative complication is now realized to be actually more prevalent among medical patients Patients with congestive heart failure are particularly subject to thromboembolic phenomena Difficulty in management rests not so much with therapy as with diagnosis A serious hiatus exists between clinical ability to recognize thrombosis and embolism and its actual incidence as demonstrated post mortem Since prophylactic anticoagulant therapy seems to provide the only safeguard against this serious complication of congestive failure W Proctor Harvey and Clement A Finch[3] (Harvard Univ) attempted to determine the safety

(3) N E gl d J M d 42 08 11 F b 9 19 0

of dicumarol® in such patients and its effectiveness in preventing thromboembolic disease

For three years patients with congestive heart failure irrespective of the heart disease were placed on dicumarol® therapy (80 patients) or in a control group (100 patients) depending on whether date of hospitalization was an even or an odd day Age sex distribution type of heart disease and frequency and severity of manifestations of congestive failure were similar in the two groups Attempt was made to regulate prothrombin time at approximately 30 per cent and daily prothrombin determinations were made throughout dicumarol® therapy

The impression was gained that dicumarol® can be safely administered to such patients provided the usual precautions are taken There was a total mortality rate during hospitalization of 17 per cent among controls and 9 per cent in the dicumarol® treated group Eight deaths among controls were believed on the basis of autopsy to have been due to pulmonary embolism whereas in patients given dicumarol® no deaths were believed due to embolism Deaths unrelated to thromboembolic disease were quite similar in the two groups

These data suggest that dicumarol® brought about significant reduction in thromboembolic disease and thus lowered mortality rate in patients hospitalized with congestive failure

Treatment of Repeated Embolism in Mitral Stenosis by Long Term Administration of Dicumarol® Since many patients with compensated mitral stenosis may live a long time except for the hazard of repeated embolism a means to prevent intracardiac clot formation without undue cost and risk of bleeding was welcomed in the discovery of dicumarol® as a practical anticoagulant Heparin for obvious reasons of price and inconvenience of application cannot be used for long periods but dicumarol® is inexpensive effective and its dosage can be controlled by careful prothrombin level determination in any reliable clinical laboratory As a means of preventing thromboembolic complications in mitral stenosis dicumarol® has not been used widely however

Irving Imber and Heinz Magendantz[4] (Boston) report the value of continued dicumarol® therapy under careful supervision in a woman aged 34 with mitral stenosis and auricular

(4) B ll N w E gl d M Cent 11 151 158 A gu t, 1949

fibrillation She had had five embolic episodes in the four months preceding dicumarol® therapy Embolic phenomena ceased after establishment and maintenance of an adequate prothrombin level

It cannot be stated certainly that dicumarol® therapy caused the sudden cessation of embolic phenomena in this patient since spontaneous remissions in such cases have been observed The sudden change from repeated serious arterial emboli during the preceding months to none after establishing the desired reduction in prothrombin level however appeared to be more than mere coincidence It is presumably necessary to continue dicumarol® therapy indefinitely in such patients

Long Term Dicumarol® Therapy is described in a case reported by Raymond L Rice Jack S Ackerman and Robert Saichek[5] (Milwaukee)

Physician 48 had an acute myocardial infarction in May 1944 A chest x ray two days later was interpreted as showing a bilateral bronchopneumonic process or changes secondary to pulmonary infarction In May 1945 he noted fever and pain in the chest which was exaggerated by deep inspiration and swallowing and persisted for two days then subsided In July 1945 he had another myocardial infarction At this time dicumarol® was given in doses adequate to keep prothrombin levels between 40 and 50 per cent for the duration of his two week hospital stay Examination of lungs two days after the acute infarction revealed scattered rales over the right base posteriorly and a diagnosis of pulmonary infarction was made In August and again in September 1945 the patient experienced acute episodes of chest pain similar to the previous attack The patient's symptoms were believed due to recurrent pulmonary emboli probably multiple in an attack and likely arising in the right ventricle It was suggested that dicumarol® be continued for several months with the hope of avoiding these recurrent episodes

Dicumarol® was given from October 1945 until June 1947 when it was decided that a trial would be made without the drug In September 1947 another acute episode of chest pain occurred The patient has remained on dicumarol® therapy since that time with no recurrence of thromboembolic episodes

Biweekly prothrombin times were taken to determine adequate dosage during the first several months the drug was used Weekly dosage totaling 500 550 mg was necessary to maintain the prothrombin level within optimal limits By September 1946 a pattern of individual response to dicumarol® seemed fairly well established and weekly then biweekly and occasionally monthly estimates were made Administration of a 100 mg dose of dicumarol® followed by

(5) Ann Int Med 32 735 745 Apr 1950

two or three daily doses of 50 mg (450 500 mg /week) obtained prothrombin levels between 37 and 18 per cent from November 1947 to the time of this report Lower levels occurred only when aspirin or sulfonamides were administered At this time gingival bleeding petechiae conjunctival hemorrhages ecchymosis of the skin hematuria and bloody stools also occurred Mild gastrointestinal disturbances seemed to precede onset of hemorrhagic phenomena and consisted of distention flatulence abdominal cramps and light to clay colored stools These episodes were avoided by reducing dicumarol® dosage during salicylate or sulfonamide therapy A total of 66 300 mg dicumarol® was taken over 40 months

Treatment with Dicumarol® in Small Continuous Doses Since dicumarol® was used first in 1941 in anticoagulant therapy intermittent application has been most frequently used The characteristic features of treatment are the large maintenance doses and long intervals between doses It is common experience that this method makes it difficult to maintain prothrombin time in what is considered a therapeutically active zone Leopold Epstein and Asger Nørholm Pedersen[6] (City Hosp of Aarhus Denmark) therefore tried other forms of dosage in 37 patients in the hope of maintaining the prothrombin index within the therapeutically effective zone (between 20 and 50)

Best results were obtained with small maintenance doses of 2 cg two to four times daily depending on the individual response In 14 of 16 patients treated in this manner the prothrombin index was reduced to the desired level between 20 and 50 An advantage of this method is that fluctuations in prothrombin time are small and easily controlled by slight alteration of dose When the index approaches 20 treatment is stopped for 24-48 hours and then resumed with smaller doses Since the index varies only slightly from day to day with this type of dosage daily reading of prothrombin time is not absolutely necessary This continuous treatment is therefore more convenient for the patient simplifies hospital work and makes possible outpatient treatment with a better margin of safety

Resection of Left Auricular Appendix Prophylaxis for Recurrent Arterial Emboli is reported by John L Madden[7] (New York City)

Case 1—Woman 38 with chronic rheumatic heart disease

(6) Act m d. S 1 136 351 8 19 0
(7) J A M A. 140 69 2 1 1 1 49

with mitral stenosis auricular fibrillation and recurrent peripheral arterial emboli which had necessitated embolectomy on two occasions was chosen as the first patient for resection of the left auricular appendix During operation the heart stopped Immediate manual massage of the heart was begun together with artificial respiration The patient recovered Hemiparesis present after operation was believed secondary to a right cerebral embolus Subsequently a decided personality change was observed but examination eight months after operation disclosed personality to be normal The patient had a spastic hemiplegic gait but walked well without support Histologic examination of the specimen revealed myocardial hypertrophy fibrosis and mural thrombus of the left auricular appendix the appendix was three times normal size

CASE 2—Man 52 was chosen for the second operation because he had had an embolic occlusion of the abdominal aorta at its bifurcation complicating chronic rheumatic heart disease with mitral stenosis auricular fibrillation and congestive heart failure Operation was uneventful Soon after operation oliguria abdominal pain and tenderness in the right upper quadrant and distention occurred but one week after operation the patient was out of bed apparently much improved However on the ninth day he complained of weakness and apprehension That afternoon he sat up to take a drink of water and suddenly died Permission for autopsy was not obtained Histologic examination of the operative specimen revealed mural thrombus of the left auricular appendix The appendix was normal in size and appearance

The commonest mode of origin of a peripheral arterial embolus is detachment of a mural thrombus located in one of the heart chambers Mural thrombi occur most frequently in cases of coronary thrombosis with myocardial infarction and in rheumatic heart disease In over 90 per cent of patients with rheumatic heart disease thrombi are located in the auricles particularly the auricular appendixes Peripheral arterial emboli occur in approximately 45 per cent of cases of rheumatic heart disease in 15 20 per cent of cases a cerebral embolus is the immediate cause of death Madden suggests resection of the left auricular appendix as a prophylaxis for recurrent arterial emboli The one indication for operation is one or more recent peripheral arterial embolic occlusions in a patient with rheumatic heart disease and mitral stenosis with or without auricular fibrillation

Early Sign of Femoral Thrombosis Gerald H Pratt[8] (St Vincent s Hosp New York City) noted three dilated sentinel veins over the tibia in over 80 per cent of patients

(8) J A M A 140 4 6 477 J 4 1949

with pathologic clotting (Figs 92 and 93) It has been proved that the thrombosis which causes pulmonary embolism originates in most instances in veins of the calf and progresses to the popliteal vein The first veins to dilate owing to this obstruction are the ones opening directly into the popliteal vein particularly branches of the anterior tibial vein The three small veins over the tibia empty into the saphenous and



F g 92 (l ft) —S t l e n d l t d th t b a n rly g f th mbo
F g 93 (ght) —Se t el Th p th ght l g p eded th t
l ft by tw da
(C te y f l att G H J A M A 140 4 6 477 J ne 4 1949)

the anterior tibial vein system are superficial and unsupported by musculature and therefore dilate very early

This sign was noted 84 times in 109 instances of thrombosis and led to an early diagnosis Other early diagnostic points are pain in the popliteal space or calf tenderness over the involved vein areas slight cyanosis of the part compared to the other parts abnormally elevated pulse rate and temperature fear of impending disaster (many patients are aware that something is wrong) very mild edema and a small nonfatal embolism (25 per cent of patients have a small embolism before a fatal one)

Fat Embolism. J L Dunphy (Boston) and Frederic W Ilfeld[9] (Los Angeles) discuss the value of x ray in diagnosis

(9) Am J S g 7 3 43 J 1949

and of oxygen in treatment of fat embolism Three conditions are necessary for development of fat embolism (1) liquid fat free in tissues (2) torn and patent veins and (3) increased local tissue pressure above the level of venous pressure Such factors may arise after fractures blast injuries burns extensive contusion of subcutaneous tissue or surgery

When *fat enters the circulation it is carried first to the* lungs Some is squeezed through the pulmonary circuit and then distributed It appears to be well tolerated by most organs except the brain It is likely that small amounts of fat enter the circulation frequently though fat embolism as a principal cause of death is rare

Presence of fat embolism should be suspected when injury to bone especially simple fractures of the tibia or femur or extensive soft tissue injuries or surgical procedures in which large amounts of fat are excised or unduly traumatized is followed by an interval free of symptoms which may vary from a few hours to 9 or 10 days and then by onset of pulmonary or cerebral symptoms or both Pulmonary manifestations may vary from moderate elevation of the respiratory rate with fever to severe pulmonary edema with dyspnea cyanosis and frothy sputum Cerebral signs vary from mild psychosis or confusion to clonic convulsions generalized ragidity and coma When both pulmonary and cerebral signs appear after a free interval diagnosis is almost unmistakable The combination of petechial hemorrhages in skin and mucous membranes with cerebral or pulmonary signs is also practically diagnostic Use of x ray in diagnosis may be helpful In the case reported by the authors films taken one day after onset of embolism showed diffuse clouding throughout both lungs a picture characteristic of acute pulmonary edema and similar to that *after myocardial infarction* Fat *in urine and* sputum is confirmatory diagnostic evidence

Though treatment of fat embolism is usually regarded as useless the authors found oxygen in high concentration to be of specific value Oxygen administered by closed B L B mask brought about dramatic improvement in their patient and continued to be beneficial throughout the first two weeks of illness

Acceleration of Linear Flow in Deep Veins of Lower Extremity of Man by Local Compression was proved experimen

tally by Joseph R Stanton Edward D Freis and Robert W Wilkins[1] (Boston) in studies of 20 subjects

METHOD —With the patient supine on the x ray table the entire leg from instep to upper third of the thigh was encased in a series of loosely fitting blood pressure cuffs or in an inflatable legging A needle was inserted into a distal vein on the dorsum of the foot To the needle was attached a three way stopcock and tubing leading to *an infusion of normal saline solution Test substances were injected* directly into the vein through the side arm of the three way stop cock After control observations were completed the limb was pres *surized by inflating the garment or blood pressure cuffs at pressures* of 20 or 35 mm Hg In two patients an additional needle was placed in the femoral vein just proximal to the upper margin of the in flatable garment and blood samples collected in oxalated tubes every four seconds Test substances used in carrying out these experiments were solutions of 35 per cent diodrast® 20 per cent decholin® sodium and 0 5 per cent Evans blue dye (T 1824)

Two observers noted through a fluoroscopic screen the time required for 4 cc of diodrast® to pass from the needle to a lead marker applied to the upper third of the calf When control observations were completed the limb was pressurized at 20 mm Hg and the procedure repeated Control mean ap pearance time was 21 78 seconds contrasted with a mean ap pearance time of 11 38 seconds during pressurization

To confirm these results by more accurate methods lead markers were fixed at specific intervals on calf and thigh and the distance between markers carefully measured so that the linear velocity in centimeters/second could be determined Se rial roentgenograms of the calf and thigh were taken at exact intervals Technical difficulties prevented this technic from yielding results that could be accurately interpreted in every experiment However in no experiment could the results be interpreted as indicating that pressurization had decreased the velocity of venous flow On the contrary in practically every experiment particularly when the major portion of the dio drast® entered the deep venous system of the leg velocity of flow was unquestionably increased

Additional corroborative evidence of the acceleration of venous flow during application of pressure was obtained by foot to tongue (decholin®) circulation times in six cases Cir culation times in all instances during pressurization were de creased Limb venous circulation time was estimated in two

(1) J Clin I t g t 8 553 558 M 1949

patients before and during application of pressure by measuring concentration of injected dye in consecutive four second samples from the femoral vein In both cases the appearance time of the dye was decidedly decreased during application of pressure

During this investigation collateral observations were made on size and shape of leg veins In young persons the deep veins of the calf were usually narrow and straight whereas in older persons the deep veins frequently exhibited saccular dilatations Veins well filled with diodrast® as viewed in serial roentgenograms frequently exhibited a measurable decrease in diameter during local compression Application of pressure usually did not alter distribution of diodrast® between superficial and deep veins but accelerated the flow in both Increasing pressure from 20 to 35 mm Hg did not cause a perceptible further increase in velocity of venous flow In six patients the velocity of venous flow was similarly accelerated whether the source of local compression was an inflatable legging an elastic stocking or a carefully applied elastic bandage

The authors suggest that the mechanism of the increase in linear velocity of venous flow during local compression is the concomitant decrease in total cross section area of the venous beds

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CEREBRAL VASCULAR DISEASE

These articles offer further evidence of the therapeutic value of stellate ganglion block in the treatment of cerebral thrombosis In view of th s the failure of cerebral blood flow to increa e following such block i of interest —Ed

Emergency Treatment of Apoplexy Despite theoretical considerations which make it seem unlikely that temporary elimination of vasomotor tonus of cerebral vessels would effectively influence deranged cerebral circulation following apoplexy Geza de Takats and G W Graupner (Univ of Illinois) believe that prompt performance of sympathetic block accelerates the phase of restitution In other words in all cerebrovascular accidents surrounding the ischemic or hemorrhagic infarct is a zone of stasis vasoparalysis and exudation of plasma

On the basis of this concept the following therapeutic

( ) P tt 164 24 248 M h 1950

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METHOD —With the patient supine on the x ray table the entire leg from instep to upper third of the thigh was encased in a series of loosely fitting blood pressure cuffs or in an inflatable legging A needle was inserted into a distal vein on the dorsum of the foot To the needle was attached a three way stopcock and tubing leading to an infusion of normal saline solution Test substances were injected directly into the vein through the side arm of the three way stopcock After control observations were completed the limb was pressurized by inflating the garment or blood pressure cuffs at pressures of 20 or 35 mm Hg In two patients an additional needle was placed in the femoral vein just proximal to the upper margin of the inflatable garment and blood samples collected in oxalated tubes every four seconds Test substances used in carrying out these experiments were solutions of 35 per cent diodrast® 20 per cent decholin® sodium and 0 5 per cent Evans blue dye (T 1824)

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(1) J Cl I t g t n 8 5 3 8 May 1949

tain cases of subarachnoid hemorrhage Anticoagulant therapy may help prevent extension of the thrombus or additional emboli and formation of thromboemboli in leg veins Oxygen therapy helps prevent or decrease cerebral anoxia and edema Vitamin K in intracranial hemorrhage decrease of intracranial pressure with hypertonic sucrose or concentrated salt free albumin and use of papaverine and/or aminophylline as vasodilators to help decrease edema surrounding the lesion may all be of aid Finally stellate ganglion block is an extremely useful therapeutic tool

Paul W Searles and William K Nowill[3] (Buffalo) compiled a series of cases of cerebral vascular accidents in which they compared a group of 55 patients on whom 127 stellate ganglion blocks were performed with a control group of 158 patients Patients were completely unselected except that after some experience it was decided not to try block in those who had grossly bloody cerebrospinal fluid since it did not appear beneficial and was thought possibly to increase bleeding

Best results with stellate ganglion blocks were obtained in cases of cerebral thrombosis of recent origin 45 per cent of 31 patients showed improvement compared with 19 per cent of the controls and mortality rate was reduced from 58 to 35 per cent Of patients with cerebral embolism 37 per cent showed improvement with stellate block Among controls no patient showed complete spontaneous remission of symptoms

The usual treatment of residual defects in the chronic stage consists of physical therapeutic measures All patients in the old or chronic group of cerebral thromboses selected for stellate ganglion block had shown no improvement of muscle function on this ordinary regime Cerebral vascular occlusion had occurred at least one month before stellate ganglion block In 43 per cent of these patients there was some improvement attributable to block therapy The authors consider this treatment of value in that it decreased disability

TECHNIC—The posterior approach appears to be the safest The patient is placed on the side with the neck acutely flexed The most prominent vertebral spinous process at the base of the neck is considered to be the seventh cervical A wheal is raised 2/ cm lateral to the interspace between the seventh cervical and first thoracic spines A needle is inserted perpendicular to the skin and advanced

(3) South M J 43 29 34 Ma h 1950

measures are recommended in acute cerebrovascular accidents In patients with cerebral embolism an oxygen tent medication for slowing of rapid fibrillation stellate block and anticoagulants are ordered In patients with cerebral thrombosis an oxygen tent venesection in case of hypertension stellate block and release of increased cerebrospinal fluid pressure are indicated In patients with cerebral hemorrhage an oxygen tent slow spinal drainage and neurosurgical consultation for possible evacuation of clots may be considered No sympathetic block need be done In all three types of apoplexy hypertonic sucrose or concentrated albumin with 5 7½ gr aminophylline given intravenously improves cerebral edema There is some evidence that aminophylline lowers cerebrospinal fluid pressure and its use is more rational than the extreme dehydration advocated for patients with cerebrovascular accidents

The authors performed stellate injections on 50 patients and obtained good response in 41 They recommend that injections be performed daily until no further improvement is noted

Cerebral Vascular Accidents Treatment by Stellate Ganglion Blocks Until recent years therapy for victims of the so called stroke or shock was empiric and these patients either died or survived with varying degrees of residual motor disability During the past 10 years a mode of treatment has evolved which has decreased both mortality and disability in cerebral vascular disease The disease may be divided into two stages acute and chronic The acute stage consists of the premonitory period of headache dizziness drowsiness and mental confusion followed by onset of paralysis of muscles of leg arm face and speech or coma If the patient survives thi period he may have chronic paralysis or muscle weakness

Treatment of patients with cerebral vascular accidents is determined by the stage of the disease In the acute stage it consists of skilled nursing care (frequent positional changes regular changes of linen to keep the patient dry treatment of pressure points oropharyngeal suction urinary bladder care adequate fluid) cautious use of sedatives and abstinence from opiates Lumbar puncture is of value as a diagnostic procedure in all cases and as a therapeutic measure in primary subarachnoid hemorrhage Antibiotics are valuable Neurosurgery may be necessary e g in ligation of the ruptured vessel in cer

cular disease or elderly patients with cerebral thrombosis Failure of cerebral blood flow to increase in these patients indicates that increased cerebrovascular resistance is not due to increased tone mediated by the sympathetic nervous system Present observations confirm those of Penfield indicating that complete removal of all sympathetic nerve fibers which enter the cranial cavity on the carotid and vertebral arteries does not appreciably reduce the number of normal intracranial perivascular nerve fibers Both studies indicate that the sympathetics do not greatly influence cerebral vascular tone

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MISCELLANEOUS

Some of the most important reports are included in this chapter The study dealing with effects of bed rest on cardiovascular function of normal subjects raises the question as to whether the harmful effects of prolonged rest in bed may not outweigh the benefits obtained in certain patient with cardiac disease The demon tration that anxiety imposes a greater load on the heart than the usual physical exertions of ordinary living has n obvious and important therapeut c implication —Ed

Effects of Bed Rest on Cardiovascular Function and Work Performance Henry Longstreet Taylor Austin Henschel Josef Brozek and Ancel Keys[5] (Univ of Minnesota) studied six healthy young men before during and after three to four weeks bed rest Performance of the cardiovascular system (at rest in the upright posture and during work) and speed co ordination and strength were measured under rigidly controlled conditions

Bed rest produced a 17 per cent decrease in heart volume and an 8 per cent decrease in transverse diameter of the heart There was a highly significant increase in resting pulse rate which averaged roughly 0 5 beats/minute/day of bed rest Pulse rate at the end of a half hour walk at 3 5 mi /hour and 10 per cent grade increased by 40 beats/minute after bed rest Bed rest had not influenced mechanical efficiency during this walk

Oxygen intake during a 90 second run at 7 mi /hour and 15 per cent grade was reduced by 730 cc oxygen or 16 per cent after 3-4 weeks bed rest This was accompanied by increases in oxygen debt and blood lactate after the run and a

(5) *J Appl d Phy* 1 2 2 3 239 N mbe 1949

until bony contact is made with the transverse process of the first thoracic vertebra The needle is then partially withdrawn redirected upward and medially and advanced approximately 1 cm deeper Injection of 1 2 cc of 2 per cent procaine or a 1 5 per cent metycaine* solution is done with repeated attempts at aspiration In two to five minutes an additional 5 8 cc. is given Successful stellate block produces the well known Horner s syndrome and a hot dry arm and hand

Cerebral Blood Flow in Vascular Disease of Brain Observations on Effects of Stellate Ganglion Block. Peritz Scheinberg[4] *(Duke Univ) used the nitrous oxide technic to* measure the cerebral blood flow to and oxygen utilization of the brain in 23 patients with cerebral vascular disease—either middle aged persons with hypertension and diabetes or patients with a history of cerebral vascular accident They were divided into those with and those without changes in mental status as a result of the disease The effect of unilateral stellate ganglion block on cerebral circulation was also studied in 19 subjects

Persons with hypertension and diabetes and those with cerebrovascular accidents and normal mental status were thought to have a relatively early stage of cerebrovascular disease They showed a moderate reduction in cerebral blood flow and increased arteriovenous oxygen difference with a resulting normal cerebral oxygen utilization Persons with alterations in mental status as a result of vascular disease of the brain were assumed to have a later stage Blood flow in this group showed a considerable decrease (38 per cent) over normal whereas arteriovenous oxygen and glucose differences were only slightly increased and normal respectively This change resulted in a fall in cerebral oxygen and glucose consumption

The decrease in cerebral metabolism is related to inability of the brain cells to extract more oxygen and glucose per unit of blood rather than to the low blood flow itself Poor cellular function is thought to result in some way from the progressive vascular disease This metabolic defect is probably related to the greatly increased resistance offered to the flow of blood by diseased cerebral vessels However unilateral stellate ganglion block produced no change in cerebral metabolic functions in normal persons patients with hypertensive vas

(4) Am J M d 8 139 147 F b ary 1950

death in 14 states In addition physicians friends places of previous employment insurance companies and credit bureaus were consulted home addresses and neighbors were visited police searched neighborhoods and notice was put in 20 news papers and broadcast over six New England radio stations By these measures 171 patients were located Pertinent infor mation was obtained from 151 of the 153 patients alive when located In 115 patients this included physical electrocardiographic and fluoroscopic examinations

From data collected it was concluded that neurocirculatory asthenia is usually a chronic disorder which does not inter fere significantly with a patient s work or social or family life nor does it cause death In this study 12 per cent of patients recovered 35 per cent had symptoms but no disability 38 per cent symptoms with mild disability and 15 per cent symptoms and moderate or severe disability In patients with this disorder there was not a high prevalence of the diseases recently said to be caused by anxiety hypertension heart dis ease peptic ulcer diabetes mellitus asthma thyrotoxicosis ulcerative colitis hysteria and schizophrenia Fewer deaths occurred in the group than were statistically expected but it is not known whether this was due to the nature of the groups used for comparison or whether it is truly a feature of the disorder

Published results of therapy in apparently similar cases managed by prolonged psychotherapy psychoanalysis and other methods such as electric convulsion procedures use of ergotamine tartrate and adrenal denervation presented no consistent or conclusive evidence that patients treated by these means get along better than patients who have had little more therapy than simple reassurance and the passage of time With reference to technic of follow up studies it is concluded that it is possible to locate and obtain co operation from most patients even 20 years after the original examination and diagnosis

Neurocirculatory Asthenia (Anxiety Neurosis Neurasthe nia Effort Syndrome Cardiac Neurosis) Mandel E Cohen[7] (Harvard Univ) summarizes present knowledge of the dis order the chief symptoms of which are breathlessness palpi tation nervousness irritability chest discomfort fatigability

(7) M Clin North America 33 1343 1364 September 1949

decrease in mechanical efficiency Maximal oxygen intake was determined in two men who had decreases of 13 and 22 per cent after bed rest

Bed rest produced striking deterioration in the cardio vascular response to posture as measured by pulse rate and blood pressure changes produced by tilting to 68 degrees on a tilt table Ataxiameter studies showed that sway was defi nitely increased by bed rest Co ordination as measured by pattern tracing suffered a small loss as the result of bed rest whereas speed of small hand movements of medium arm and hand movements and of gross body and arm movements did not deteriorate Grip strength was not influenced by bed rest and back strength deteriorated only slightly

After bed rest the rate of recovery of various functions was roughly proportional to the extent of deterioration in bed rest Strength co ordination and postural sway returned to normal early (four days) blood lactate after exhausting work and oxygen cost of exhausting work at an intermediate time (two weeks) pulse rate during grade walking and oxygen intake during exhausting work late (between two and five weeks) and cardiovascular response to posture very late (after seven weeks) In one man the effect on the principal com ponents of fitness of a hemorrhaphy with bed rest for three weeks was of the same order of magnitude as bed rest alone

The authors concluded that the deconditioning due to bed rest has special characteristics with major loss of perform ance ocurring in the cardiovascular system

Neurocirculatory Asthenia (Anxiety Neurosis, Effort Syn drome, Neurasthenia) 20 Year Follow up Study of 173 Patients is reported by Edwin O Wheeler Paul D White Eleanor W Reed and Mandel E Cohen[6] (Harvard Univ) For purposes of this study symptoms of neurocirculatory asthenia included breathing trouble and symptoms from two of the following three groups (1) palpitation or chest pain (2) nervousness dizziness faintness attacks or spells and (3) fatigue tiredness or limitation of activity Records of all pa tients examined by White before 1928 were reviewed Of these 173 met the diagnostic criteria Patients were located by search of telephone and street directories alumni and pro fessional lists files of licenses and records of divorce and

(6) J A M A 142 878 889 M 5 1950

serious consideration of the patient s condition adequate medical examination reassurance and elimination of relevant provoking factors frightening diagnoses unnecessary therapeutic procedures such as drugs surgery and unnecessarily prolonged psychotherapy

Genesis of Heart Sounds is reviewed by Oscar Orias[8] (Cordoba Argentina) *At least four sounds may occur under normal conditions* during the heart cycle Two the classic first and second sounds are heard in any living person A third heart sound may be heard during early diastole in many young persons after the second sound and the fourth sound also called auricular takes place and may often be heard immediately before the first sound during auricular systole

There is experimental and clinical evidence that the following events produce vibrations contributing to formation of the first sound muscular contraction and tension of the ventricular walls at onset of ventricular systole (muscular factor) closure of the auriculoventricular valves (valvular factor) movements and distention caused by the ejection of blood from ventricles into arteries (vascular factor) and residual vibrations due to the preceding auricular contraction (auricular factor) These factors are not listed in order of their relative importance for it varies according to conditions and with the site of auscultation However almost everyone agrees that the *valvular factor is the most important*

Origin of the second sound is much simpler than that of the first All anatomic clinical and experimental observations have adduced proofs in favor of the idea that closure of the semilunar valves is the essential cause of the second sound which is the acoustic expression of vibrations set up at this moment in the valves in the walls of the artery and also in the blood column itself In the ordinary conditions in which auscultation is made the sounds originating in the aorta and the pulmonary artery respectively are heard as only one sound owing to summation In cases of asynchronous closure of the semilunar valves a reduplicated or split second sound is the result

The third heart sound is produced in the final moments of rapid ventricular filling The hypothesis has been advanced that *the third heart sound is caused by vibrations of the ven*

(8) N w E gl d J M d 241 763 769 N 17 1949

and spells of dizziness faintness or anxiety attacks There is a chronic familial form with remissions and exacerbations and there is also an acute form The disorder is characterized by appearance of many symptoms but few signs Patients may complain of choking and smothering spells rapid heart beat pain in the chest nervousness getting tired easily irritability dizziness or heart trouble Systematic and thorough questioning reveals many symptoms in addition to the chief complaint Difficulty in doing hard work is almost universal as is difficulty in handling emotion provoking situations Review of systems reveals headaches blurred vision and giddiness Breathing difficulties are almost universal Sighing respiration is characteristic Dyspnea on exertion or even while sitting down is common as is chest discomfort The first symptoms rarely appear before age 18 and rarely after 35 Approximately twice as many women as men with this disorder are seen by physicians There is a high familial prevalence

Signs of the disorder include slight and inconstant tachycardia slight tachypnea sighing respiration flushed face and neck tremor of outstretched fingers and brisk patellar and Achilles deep tendon reflexes Results of standard clinical laboratory procedures are within normal limits Course of the illness is mild in most patients There may be remissions and exacerbations Despite symptoms of palpitation breathlessness and apprehensiveness a 20 year follow up study of 173 patients revealed that they did not show an unusual incidence of diseases such as hypertension and peptic ulcer which are supposed to develop as a result of anxiety Neurocirculatory asthenia did not predispose to any other disease or to early death

There is convincing evidence that this disorder represents a fairly common diagnostic entity in contrast to most other psychiatric illnesses which are probably rare Quantitative and objective findings bear out the patients stories Patients find hard work difficult and hard work studies (judged by treadmill and 20 in step tests) show definite abnormalities They complain of poor breathing and studies of respiration show measurable abnormalities They complain of pain and discomfort and quantitative studies show responses to various types of discomfort at significantly lower stimulus levels

There is no specific treatment Management s

serious consideration of the patient s condition adequate medical examination reassurance and elimination of relevant provoking factors frightening diagnoses unnecessary therapeutic procedures such as drugs surgery and unnecessarily prolonged psychotherapy

Genesis of Heart Sounds is reviewed by Oscar Orias[8] (Cordoba Argentina) At least four sounds may occur under normal conditions during the heart cycle Two the classic first and second sounds are heard in any living person A third heart sound may be heard during early diastole in many young persons after the second sound and the fourth sound also called auricular takes place and may often be heard immediately before the first sound during auricular systole

There is experimental and clinical evidence that the following events produce vibrations contributing to formation of the first sound muscular contraction and tension of the *ventricular walls at onset of ventricular systole (muscular* factor) closure of the auriculoventricular valves (valvular factor) movements and distention caused by the ejection of blood from ventricles into arteries (vascular factor) and residual vibrations due to the preceding auricular contraction (auricular factor) These factors are not listed in order of their relative importance for it varies according to conditions and with the site of auscultation However almost everyone agrees that the valvular factor is the most important

Origin of the second sound is much simpler than that of the first All anatomic clinical and experimental observations have adduced *proofs* in favor of the idea that closure of the semilunar valves is the essential cause of the second sound which is the acoustic expression of vibrations set up at this moment in the valves in the walls of the artery and also in the blood column itself In the ordinary conditions in which auscultation is made the sounds originating in the aorta and the pulmonary artery respectively are heard as only one sound owing to summation In cases of asynchronous closure of the semilunar valves a reduplicated or split second sound is the result

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(8) N w E gl d J M d 241 763 769 N 17 1949

tricular walls caused by sudden distention by the inrush of blood from the auricles in the final moments of rapid ventricular filling By the term ventricular walls no distinction is implied between muscular and tendinous structures or valves Furthermore although the cause given is stressed as the principal one subsidiary factors should not be excluded

During auricular activity various phenomena may produce a sound Acoustic vibrations may be produced during auricular contraction by the muscular contraction itself by tension of auricular walls passage of blood through valvular orifices distention of ventricular walls by the inrush of blood from the auricles or by friction of the auricle against neighboring structures All these factors probably combine in different proportions to produce the auricular sound

In discussion William Dock stated that in his opinion the first sound originates in the auriculoventricular and the second in the semilunar valves This opinion is based on experiments in which a piezoelectric device was inserted into dogs hearts through the carotid artery or jugular vein to record the pressure synchronously with the electrocardiogram Such records show clearly that the first sound is intense only at the auriculoventricular orifice and the second sound is intense only at the aortic orifice Likewise all the third and fourth sounds and gallops are due to tension of the auriculoventricular valves The basal first sound may contain elements or rarely a distinct split sound owing to the shock in the wall of the great arteries usually in man the pulse wave causes no sound in the aorta and in dogs in which brachial and femoral vessels have normally a pulse sound the aorta has none or a very feeble one Most split first sounds are due to ventricular asynchrony The ventricular muscle is a good sound damper as is the blood itself The great vessels transmit sound fairly well

Circulatory Dynamics before and after Exercise in Subjects with and without Structural Heart Disease during Anxiety and Relaxation Ian P Stevenson Charles H Duncan and Harold G Wolff[9] (Cornell Univ) made a study of heart rate blood pressure and cardiac output before and after a standard exercise test in persons with and without structural heart disease who had varied emotional disturbances

(9) J Cl I tg to 8 1534 1543 N mbe 1949

In patients who were slightly disturbed emotionally average cardiac outputs were greater before and after exercise than in those who apparently were undisturbed The difference was largely attributable to increases in stroke volume In patients with striking overt anxiety symptoms average cardiac outputs were greater before and after exercise than in those who were slightly disturbed emotionally The difference was largely attributable to greater increases in heart rate Generally there was close correlation between symptoms such as dyspnea palpitations and weakness on exertion and impaired exercise tolerance

In 10 patients with structural heart disease similarly studied the same relationship was found between emotional disturbances and signs of effort intolerance The symptoms were similar to those usually associated with cardiac failure but they often disappeared with the abolition of anxiety although structural defects in the heart were still present Changes in emotional state were accompanied by changes in exercise tolerance in seven patients alterations in exercise tolerance were observed in less than an hour

The authors concluded that impaired exercise tolerance during emotional disturbances apparently results from exaggerated cardiac mobilization in response to symbolic stimuli In the early stages of cardiac mobilization increased cardiac output is mainly achieved by increases in stroke volume in more advanced stages this increase results more from excessive increases in heart rate Ordinary physical exertions of everyday life performed during periods of relaxation and security impose little extra work on the heart compared to the cardiac mobilization associated with anxiety The increased cardiac work and excessive tachycardia at rest and in response to exercise during anxiety may be related to the increased susceptibility of patients with tachycardia to development of structural heart disease

Some Cardiologic Problems of the Tropics are the subject of statistical analysis and discussion by E Garcia Carrillo[1] (San Jose Costa Rica) Among 8 000 autopsies on patients in Costa Rica mortality of 9 6 per cent was attributable to cardiovascular disease The types of cardiovascular disease which caused death were found to be in the following proportion

(1) Am J M Sc 217 619 6 6 J 1949

:onary artery 46 1 per cent rheumatic heart including cification of aortic valve 20 per cent, syphilitic heart 19 1 ; cent and cardiopulmonary heart 5 per cent Rarer causes re conditions due to malnutrition ancylostomiasis and ike venoms The rarity of myocardial infarct (0 2 per cent) attributed to the low fat and caloric content of the diet

Despite statements to the contrary rheumatic heart dis e was found to be common in these inhabitants of the pics On the other hand subacute bacterial endocarditis s rare It is thought that the persistence of infection in sons with rheumatic heart disease made them immune to :terial endocarditis

Myocarditis from Chagas disease or malaria was not nd among these patients However heart failure frequently ulted from anemia caused by malaria or ancylostomiasis addition the immobility of patients with ancylostomiasis disposed them to thrombosis and embolism Although try osomiasis is found in Costa Rica the author had no expe ice with patients suffering from this disease In trypano niasis myocarditis results from parasitic invasion of the ocardium Diagnosis is made by complement fixation :tion

Serial electrocardiograms were made of 11 patients who been bitten by snakes When toxic symptoms were pres ECG s showed low rounded T waves depressed S T junc s and prolonged QT intervals Because muscle treated i snake venom is known to lose potassium it is suggested the electrocardiographic changes after poisonous snake s are the result of hypopotassemia

Tussive Syncope Observations on Disease Formerly Called yngeal Epilepsy, with Report of Two Cases, are presented Villiam S McCann Robert A Bruce Frank W Lovejoy Paul N G Yu Raymond Pearson Ernest B Emerson rge Engel and John J Kelly[2] (Rochester N Y)

:ASE 1—Man 42 had repeated episodes of fainting associated coughing for the past three years When he was recumbent i pressure was 115/88 and on standing 122/90 Results of i studies glucose tolerance tests lumbar puncture electroen alography and electrocardiography were normal Massage of arotid sinus hyperventilation and venous congestion of the head uced by a pressure cuff around the neck at 50 mm Hg did not

2) A h I t M d 84 845 856 Dec mbe 1949

cause syncope Fluoroscopic chest examination showed decreased diaphragmatic excursion Total lung volume was reduced to 85 per cent of the predicted value whereas the volume of residual air was 30 per cent of the total capacity An exercise tolerance test showed considerable hyperventilation and diminished respiratory efficiency

Cardiac catheterization showed the usual decrease in net pulse pressure in the right ventricle in the Valsalva maneuver with reduction in systemic pulse pressure and also the extraordinary pressures that could develop inside the right ventricle during a paroxysm of coughing Many pressures were over 200 mm Significantly high pressures were sustained long enough to demonstrate pronounced reduction in systemic arterial pressure to 60 systolic and 50 diastolic To ascertain whether the pressure in the right ventricle during coughing was entirely due to increased intrathoracic air pressure or partly due to spasm of the pulmonary artery cardiac catheterization was repeated and a bronchoscope placed in the trachea No laryngeal or bronchial obstruction was seen In these circumstances the patient was unable to perform the Valsalva maneuver He could cough with considerable expulsive force and pressure in the right ventricle rose as high as 250 mm Endotracheal air pressure after removal of the bronchoscope was as high as 200 mm with coughing Although the patient was able to maintain the Valsalva experiment for 34 seconds he did not lose consciousness

Two months later he returned for further studies He had been coughing less and had had no further syncopal attacks At this time pressures in the right ventricle and pulmonary artery were normal Diastolic pressure in the right ventricle rose to 255 mm with coughing but there was no loss of consciousness Vasodilating effects of amyl nitrite tetraethylammonium chloride and aminophylline were investigated The first two caused the sensation of peripheral tingling but no other effects After only 0 09 Gm aminophylline U S P intravenously the patient had pain in the left side of the chest aggravated by deep breathing It promptly disappeared with oxygen therapy

Case 2—Man 49 had had several syncopal attacks after severe bouts of coughing He was short and plethoric with abdominal obesity Determination of lung volumes revealed a moderate amount of emphysema with increase of residual air to 46 per cent of total capacity Cardiac catheterization revealed pressures up to 270 mm in the right ventricle with mild coughing

In Case 1 it was fairly well established that syncope and convulsions coincident with paroxysms of coughing or the Valsalva maneuver were caused by congestion of the cerebral veins decreased cardiac output and anoxemia Studies to elucidate the mechanism of the pressures in the right ventricle with coughing were inconclusive The fact that the same high pressures which occurred in the right ventricle during cough

ing were produced with a bronchoscope in the trachea pointed to the possibility of reflex spasm of the pulmonary artery Importance of nicotine inhaled during smoking in producing these reactions is suggested Application of nicotine to the sympathetic ganglions supplying the lungs of experimental animals causes vasoconstriction Whether with excessive cig aret smoking nicotine could be absorbed in sufficient quantity to cause pulmonary vasoconstriction is questioned The au thors propose the term tussive syncope for this syndrome to replace the term laryngeal epilepsy because the syncopal re sponse is dependent on circulatory disturbances due to cough ing and is not due to epilepsy

Treatment of Acute Nonspecific Pericarditis with Aureo mycin This condition is usually preceded by an upper respira tory tract infection or sore throat but there are no evidences of active rheumatic infection in the joints or heart Similarly other causes for pericarditis such as tuberculosis myocardial infarction and uremia are absent Onset is generally abrupt with fever malaise and substernal or precordial pain which is worse on deep breathing movement of the trunk or swal lowing Assumption of the sitting posture or leaning forward gives partial relief from pain A pericardial friction rub is heard early and the classic electrocardiographic patterns of acute diffuse pericarditis appear in most instances Pericardial effusion may develop Treatment has been limited to bed rest and relief of symptoms until this relatively benign disease has run its course usually in two to four weeks

The possibility that acute nonspecific pericarditis might be caused by a virus and the favorable effects obtained with aureomycin in virus diseases suggested to M Taubenhaus and William A Brams[3] (Michael Reese Hosp) that this antibiotic might prove beneficial Aureomycin was administered to two patients in whom bed rest other antibiotics and other thera peutic measures failed to give relief and to a third patient early in the course of pericarditis Prompt and impressive im provement with rapid recovery occurred in all Though no final conclusions can be drawn from this small group the striking results are suggestive and are reported in the hope that they will stimulate others to make further studies of this comparatively rare disease

(3) J A M A 142 973 975 Ap 1 1950

Clinical Aspects of Endocardial Myxoma Situated in Left Atrium are described by Gosta Von Reis[4] (Stockholm) Neoplastic growth within the heart is a rare phenomenon in most instances being due to metastases arising from tumors elsewhere in the body Primary cardiac tumors are rare Among the latter the pedunculated endocardial myxomas seem to be the commonest the site affected usually being the left atrium

When such myxomas reach a certain size they produce a clinical picture strongly suggesting mitral defect chiefly stenosis The picture differs somewhat from that of stenosis however for the following reasons The patient s history reveals no definite cause for the alleged organic defect such as rheumatic fever sepsis etc Initially patients are but slightly inconvenienced by symptoms but as soon as signs of cardiac incompetence appear the condition is liable to prove fatal in a short time Auscultatory findings vary considerably These are probably due to changes in the topical interrelationship between the polyp and the mitral orifice Attack of Adams Stokes type seem to be an invariable feature without demonstrable transition into complete block In all probability these attacks occur when the polyp has attained such a size that it may temporarily obstruct the orifice When the patient s position *is changed the polyp may slide back from the orifice* circulation being re established and cerebral anemia alleviated High sedimentation rate without positive blood cultures is a frequent observation An illustrative case follows

Woman 37 had been known to have a cardiac murmur since childhood but had no symptoms until about age 30 when sudden onset of tachycardia without preceding symptoms occurred followed by palpitation and dyspnea Valvular disease was diagnosed and digitalis prescribed but fatigue and dyspnea prevented her working after age 31 There was no history of rheumatic fever At 36 diagnosis of mitral incompetence was made At that time there was a presystolic murmur in the apical area where the first sound was doubled as well as short systolic and a suggestion of diastolic murmur near the apex The second pulmonic sound was accentuated and systolic blood pressure was 105 Sedimentation rate was 56 mm

One year later dyspnea had increased markedly and there was labial cyanosis but no edema No definite cardiac murmurs were heard at this time X ray revealed a fairly pronounced enlargement of the left atrium and right ventricle as well as evidence of pulmonary stasis An electrocardiogram showed prolonged conduction time marked right ventricular preponderance and slightly expanded

(4) A t m d S d 133 214 219 1949

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massive myocardial metastases had flattened the T wave and left P Q R and S deflections unchanged Auricular fibrillation bundle branch block atrioventricular dissociation and nodal rhythm were encountered These phenomena are particularly helpful in diagnosing cardiac metastasis

Study of Effect of Adrenocorticotrophic Hormone (ACTH) on Experimental Cardiovascular Lesions Produced by Anaphylactic Hypersensitivity Various observations have suggested *that anaphylactic hypersensitivity may be an important* factor in the pathogenesis of the collagen vascular diseases Because adrenal cortex hormone has produced dramatic effects in two diseases of this group Morgan Berthrong *Arnold R Rich and Paul C Griffith*[6] *carried out experiments to* determine whether it would affect development of the lesions of periarteritis nodosa the one member of the group now definitely known to be producible by anaphylactic hypersensitivity

Procedure—Forty male albino rabbits were sensitized by a single intravenous injection of 10 cc sterile horse serum/kg body weight (This sensitizing procedure has been used in studies on the experimental production of periarteritis nodosa and rheumatic like cardiovascular lesions) On the same day intramuscular injections of ACTH were begun Since quantitative response of the rabbit to ACTH is not definitely known an initial dosage/kilogram body weight about five times that given to produce therapeutic effects in man was used. Treated animals received 5 mg ACTH every six hours during the first week Then because some animals lost considerable weight dosage for these was reduced from 20 mg /24 hours to 5 mg and for the other animals to 10 mg On the thirteenth day dosage was increased to 10 mg /24 hours for animals which had exhibited the greatest weight loss and to 20 mg for the others This dosage was maintained for 15 18 days when the animals were killed

All treated and control animals showed hypersensitivity to horse serum as revealed by positive skin tests Activity of ACTH was indicated by enlargement of the adrenal glands in the treated group Average weight of the glands in this group was 47 per cent greater than that in the controls Well marked vascular or cardiac lesions or both were found in 18 of the 20 untreated controls whereas such lesions were found in only 5 of the 20 animals treated with ACTH Though these results strongly suggest that ACTH has an inhibitory effect on development of cardiovascular lesions of hypersensitivity

(6) B II J hns Hopkins H p. 86 131 140 March, 1950

P waves Blood cultures were negative despite fever and elevated sedimentation rate. Three attacks of unconsciousness during which the patient was pulseless occurred she died during a fourth attack. Autopsy revealed an endocardial myxoma of the left atrium

Heart Tumors During 1937 45 Achille Piotti[5] (Univ of Zurich) observed 30 cases of tumor metastasis to the heart—23 carcinomas and 7 sarcomas Clinical diagnosis was made in two cases of pericarditis caused respectively by carcinoma and sarcoma metastasis in all other cases the observations were made at autopsy Twelve patients showed signs of cardiac insufficiency diagnosis of myocardial degeneration and cardiac insufficiency was made eight times and of myocarditis and cardiac infarct once each There were 17 men and 13 women in the series the difference due to the higher incidence of bronchial carcinoma in men In the 23 cases of carcinoma the primary tumor was found in the bronchi (six times) lungs (twice) breast kidneys stomach pancreas colon and pleura The left side of the heart was more often involved than the right Pulmonary inflammation occurred in 11 cases of which 6 were bronchial and 2 lung carcinomas Pulmonary abscess pyelonephritis and paranephritic abscess were other associated phenomena

Tachycardia was the most frequent and persistent symptom Cyanosis was present when the pulmonary artery or mitral valve was compressed by a tumor Precordial pain occurred when the metastases penetrated into the pericardium Other symptoms included gallop rhythm presystolic sound over the apex pericardial rub facial edema and edema of the upper half of the body

Electrocardiographic changes are not always due to the metastases but are sometimes associated with an inflammation (pneumonia pulmonary abscess etc) In such cases the small tumor buds in the heart have no connection with the massive electrocardiographic changes The ECG was normal in six patients and corresponded with the anatomic findings in five because the cardiac metastases were extremely small or located at an indifferent site The ECG was of the external layer type in three cases the tumor tissue had involved the pericardium In several ECG s with flattened T wave or depressed S T segment no toxic inflammatory causes could be found

(5) C rd l g a 14 129 190 1949

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(6) B ll J h H pk H p 86 131 140 M h 1950

further studies are necessary before such a conclusion can be regarded as established

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KIDNEY

The importance of potassium deprivation and less frequently of potassium excess in clinical medicine has begun to be realized only during the past few years The first of the following articles should therefore be read with e pecial care The reader s attention is also called to the articles on peritoneal irrigation and intestinal dialysis as well as to the discussions of lower nephron nephrosis —Ed

Clinical Potassium Problems are discussed by Helen Eastman Martin Maxine Wertman Leola Westover D G Simonsen and John W Mehl (Univ of Southern California) Of 390 serum potassium determinations made during one month in a large county hospital 24 per cent were low and 2 6 per cent were high With one exception high serum potassium values were found in patients with uremia and were due to renal retention of potassium Low serum potassium values on the surgical service were usually due to inadequate intake of potassium postoperatively resulting from prolonged use of parenteral fluids without potassium combined with nasogastric suction and alkalosis On the medical service conditions associated with low serum potassium levels were poor intake of food due to wasting diseases prolonged use of intravenous feedings without potassium diabetic acidosis under treatment Addison s disease treated with desoxycorticosterone acetate and acute pancreatitis

In the average diet there is 1 3 Gm potassium (meat nuts vegetables fruit milk) Urinary output of potassium about equals intake if cellular levels and renal function are normal Extracellular concentration though low appears necessary for activation of acetylcholine and transmission of the electric impulse along nerves or across the myoneural junction The great bulk of body potassium is in the cells where it is the major cation Two thirds of cellular potassium is bound to protein and does not diffuse The remainder passes in and out of the cell

The three mechanisms which can cause shifts in serum potassium levels are changes in intake changes in output and

(7) Cal forn a Med. 72 133 141 M eb 1950

shifts between cells and serum Inadequate intake of potassium is the most frequent clinical cause of low serum and cellular potassium levels Increased excretion of potassium in urine is related to increased nitrogen excretion due to any cause (increased tissue breakdown due to infection neoplasm uncontrolled diabetes starvation and traumatic and post operative states) Though normally only a small part of potassium is excreted in stool in cases of diarrhea or fistulas sizable losses may occur Shift from serum to cells occurs during nitrogen and carbohydrate anabolism Intensive insulin therapy of diabetic acidosis causes serum potassium to fall presumably because of a movement of potassium into the cell with carbohydrate Intensive glucose treatment in the non diabetic may also cause a shift of potassium into the cell In familial periodic paralysis there occurs a spontaneous shift from serum to cells Testosterone causes a shift of potassium into cells during protein anabolism Potassium moves out of the cell in both acidosis and alkalosis

In general low serum potassium levels are associated with decreased potassium concentrations in the cell There are a few exceptions In familial periodic paralysis the muscle levels of potassium are normal with a low serum level This also occurs following use of testosterone In severe dehydration in untreated diabetic acidosis the muscle levels of potassium may be low and serum levels elevated This may also occur during intravenous therapy of low serum potassium levels due to any cause Low muscle levels of potassium are found in myotonia congenita and nutritional muscular dystrophies

Symptoms and signs of low serum potassium are muscle weakness irritability paralysis tachycardia (rarely bradycardia) dilatation of the heart with gallop rhythm and electrocardiographic changes Some patients died of paralysis of respiratory muscles Muscle paralysis related to low serum potassium level usually affects first the muscles of the trunk and extremities The authors believe that patients with serum potassium levels under 12 mg/100 cc show some degree of muscle weakness Tachycardia is prominent in most patients with serum potassium levels under 10 mg/100 cc Dilatation of the heart systolic murmurs and gallop rhythm develop in some patients These signs which usually disappear rapidly

with correction of the potassium deficit, suggest at least functional myocardial impairment Low serum potassium levels are associated with delayed A V conduction prolonged QT intervals and inverted low amplitude or flat rounded T waves

Symptoms and signs of high serum potassium levels are usually masked by uremia Patients with potassium levels over 35 mg/100 cc observed by the authors have all died of cardiac standstill Between serum potassium levels of 25 and 30 mg/100 cc T waves become tall and peaked At about 35 mg/100 cc P waves disappear and QRS complex widens With potassium level between 40 and 50 mg/100 cc ventricular complexes become increasingly bizarre and ventricular fibrillation develops

The authors give potassium to all patients with serum potassium levels under 10 mg./100 cc For oral administration enteric coated tablets of potassium chloride (0 3 Gm) and a 1 per cent solution of potassium chloride have been used For adults 4 12 Gm KCl daily is given orally in divided doses until serum deficit is corrected Potassium chloride can also be given as a retention enema (5 10 Gm as a 1 per cent solution) Potassium for intravenous or subcutaneous administration has been given as a 0 1 per cent solution of KCl Potassium chloride is prepared in vials (1 Gm in 15 cc distilled water) and added to 1 000 cc parenteral fluid which is given slowly over two three hours Correction of potassium deficit required one to four days and 7 22 Gm KCl It is routine practice to give all patients in severe diabetic acidosis if renal function is adequate 1 Gm KCl in 1 L isotonic saline intravenously at the fourth hour of therapy and 12 Gm KCl orally in divided doses during the first 24 hours starting at the fourth hour

Many fatalities associated with uremia are actually due to the effect of high serum potassium If the renal lesion is potentially reversible reduction of serum potassium may be lifesaving Several methods have been advocated glucose and/or insulin to shift potassium into cells large saline infusions to wash out potassium in urine or correct extracellular sodium deficits calcium to antagonize potassium effect on the heart peritoneal lavage or artificial kidney to clear potassium from serum

Relation of Glomerular Filtration Rate and Sodium Tubular Rejection Fraction to Renal Sodium Excretion Renal regulation of sodium output is presumably mediated through the rate of sodium filtration and the fraction of filtered sodium which escapes tubular reabsorption If the fraction rejected by the tubule were constant sodium output would be fixed by filtration rate and an exact linear relation would exist between the two parameters Conversely if filtration rate were constant sodium excretion would be perfectly correlated with the fraction rejected Variability in both filtration rate and rejection fraction would provide an intermediate situation in which one or other of these functions would be the major but not sole renal agent for sodium output regulation D M Green W C Bridges A D Johnson J H Lehman F Gray and L Field[8] (Univ of Washington) attempted to determine which of these situations best accorded with observations on sodium output relations in man The question of particular interest was not why one subject excreted more sodium than another but how it was accomplished and whether or not the observed differences in output could be primarily explained by variations in filtration rate or by differences in tubular reabsorption

Sixty hospitalized patients selected to provide a representative cross section of filtration rates were studied Most had essential hypertension glomerulonephritis arteriosclerotic heart disease or toxemia of pregnancy Dietary sodium intake was sufficiently varied to insure a wide range of excretion rates

There was high correlation between rate of sodium excretion and the magnitude of the tubular rejection fraction No significant relation to filtration rate was established Variations in sodium output of 10 50 fold were observed at nearly identical rates of filtration There was no evidence that the relations had been significantly influenced by use of mannitol in clearance measurements

Renal Blood Flow and Glomerular Filtrate in Initial Stage of Acute Glomerulonephritis François Reubi[9] (Univ of Bern) used the clearance method to study four patients with acute nephritis who were sent to him as soon as diagnosis was

(8) Am J Phy iol 160 306-310 F bru ry, 1950
(9) S hw m d W h sch 9 896 899 S pt. 24 1949

made in one the first determination was made 48 hours after the appearance of palpebral edema He has largely followed the technic of Goldring and Chasis using para aminohippurate (PAH) to determine the effective blood flow (expressed in plasma) and sodium thiosulfate for the glomerular filtrate

METHOD —The patient fasting and recumbent is given 60 90 cc of 10 per cent sodium thiosulfate and 2 cc of 20 per cent PAH and these substances diluted with physiologic serum are administered intravenously by the drip method during the entire test to insure an approximately constant blood level The bladder is provided with an indwelling catheter and is emptied and rinsed out at the end of each period of collection The two or three periods last about 20 minutes each Toward the middle of each period blood is taken A sample of urine and one of blood taken before the test serve to determine control values Analyses for PAH are done by the method of Bratton and Marshall for the thiosulfate by that of Newman and co workers

In one patient renal extraction of the hippurate was determined by catheterization of the renal vein Blood was taken simultaneously from the sound and from a peripheral vein a few minutes after injection of 4 cc PAH Renal extraction is normally 0 94 which means that the kidney of a healthy subject extracts nearly completely the PAH it receives and that the clearance of PAH (apparent flow) equal to 94 per cent of the real plasmatic flow may be assimilated without appreciable error This ceases to be true when the extraction becomes significantly lower

Reubi found that during the first and second weeks the glomerular filtrate may reach extremely low values which gradually become normal with recovery In the only patient studied on the third day it was still subnormal and did not change until later The elevation of nonprotein nitrogen seems to be proportional to the reduction of filtrate There was no relation between the size of the filtrate and the presence of edema

During the first and second weeks the apparent renal blood flow (clearance of PAH) may be normal or lowered In one case in which it was low the extraction of PAH measured by catheterization of the renal vein was also low (0 607 instead of 0 94) this means that the real flow was much higher than the apparent flow and that it is probably normal or subnormal in all cases There is often a hyperemia from the third week on There is no correlation between the renal blood flow and the arterial tension in acute nephritis

The filtered fraction of the plasma is regularly decreased

from the sixth day on. It was normal on the third day in the only case in which it was measured so early. The decrease in the extraction of hippurate probably indicates a temporary tubular lesion.

Clinical and Pathologic Study of Renal Disease. Diseases Other than Nephritis. Robert Platt and J. Davson[1] (Manchester Univ.) studied 188 patients with renal disease. Clinicopathologic diagnoses are shown in the table.

Among patients with pyelonephritis a correct clinical diagnosis was usually suggested by history of chronic or recurrent

Clinicopathologic Diagnosis in 188 Cases of Renal Disease

Diagnosis	Cases
Glomerulonephritis	48
Pyelonephritis	26
Malignant hypertension	24
Benign hypertension	16
Periarteritis nodosa	15
Hydronephrosis	11
Diabetic glomerulosclerosis	9
Hypoplastic kidney	[illegible]
Dehydration or anoxia	10
Pregnancy kidney	2
Amyloid disease	3
Myelomatosis	3
Disseminated lupus erythematosus	2
Pheochromocytoma	1
Renal tuberculosis	1
Scleroderma	1
Miscellaneous	7

urinary infection. Because urine was frequently normal or revealed no abnormality except albumin, incorrect diagnosis of malignant hypertension was often made. Almost two thirds of the patients were under 40, before which malignant hypertension seldom occurs. When renal failure of pyelonephritis is unaccompanied by severe hypertension, chronic uremic symptoms sometimes lead to a diagnosis of anemia. In younger patients changes in mineral metabolism due to prolonged renal failure may produce the syndrome of renal rickets.

A contracted and granular kidney is easily recognized as the result of chronic pyelonephritis when evidence of urinary obstruction such as an impacted calculus, hydronephrosis or dilated ureter is also present. Variation in size between the two kidneys may be helpful in diagnosis of chronic pyelone

(1) Q. J. Med. 19:33-55, Jan. 1950.

phritis Weights of kidneys were recorded in 14 of 26 cases of pyelonephritis In seven one kidney weighed at least twice as much as the other Average combined weights of kidneys in the 14 cases was 110 Gm compared with 152 Gm in 8 cases of slowly progressive glomerulonephritis Hypertension was present in 14 of 25 patients with pyelonephritis Because of the essentially patchy involvement of renal parenchyma by the pyelonephritic process examination of a single block of kidney may show only changes regarded as secondary to hypertension whereas other areas may show changes characteristic of chronic pyelonephritis Examination of numerous blocks of tissue in contracted kidneys is essential

Principal clinical criteria by which the authors distinguished the malignant type of hypertension were papilledema high diastolic blood pressure and renal failure The diagnosis is never made without the first two the third inevitably ensues unless the patient dies prematurely of cardiac or cerebral complications Most cases of so called malignant hypertension in young persons were secondary to some pre existing renal disease Clinical diagnosis of malignant (essential) hypertension was suggested by absence of any history of pre existing renal disease (including urinary infection) presence of hypertension preceding albuminuria and renal insufficiency characteristic age incidence (35 59 in present series) and family history of hypertension At autopsy left ventricular hypertrophy was found in all cases weight of the heart ranging from 380 to 720 Gm Left ventricular hypertrophy associated with kidneys which are scarcely if at all contracted and which show characteristic reddish yellow cortical mottling indicates malignant hypertension A history of pyrexia leukocytosis rheumatic pains etc should suggest periarteritis nodosa Careful search should be made for vascular nodules especially on coronary and mesenteric arteries and numerous organs must be sectioned

Of 11 patients with hydronephrosis 9 had hypertension In one blood pressure was materially lowered by operation but not to normal In three patients hydronephrosis was unilateral the other kidney showing only the changes of malignant nephrosclerosis In presence of uremia intravenous pyelograms were useless as kidneys at this stage were unable to concentrate diodrast* Retrograde pyelography was unjusti

fiable because of the possibility of precipitating fatal urinary infection Correct diagnosis could sometimes be made by the history or by palpation of the kidneys

The fully developed syndrome of diabetic glomerulosclerosis with gross albuminuria general edema hypoproteinemia hypertension retinopathy and renal failure is indistinguishable clinically from severe nephritis except for presence of pre-existing diabetes and for the fundus oculi which often shows a mixture of the hypertensive and diabetic types of retinopathy Heavy albuminuria with deteriorating renal function in a patient with a long history of diabetes is sufficient to establish diagnosis and to predict the finding of typical Kimmelstiel Wilson bodies in the glomeruli Clinical diabetes was proved in eight of nine patients who showed these lesions

Of nine patients with renal hypoplasia hypoplasia was unilateral in four In three of these nephrectomy was performed because severe hypertension was found with a normally functioning kidney on one side and a nonfunctioning kidney on the other In one operation resulted in complete cure in the others it was unsuccessful in relieving hypertension In each case the kidney although small had a relatively smooth surface and did not appear to be grossly contracted Therefore diagnosis of renal hypoplasia was made despite superimposed chronic pyelonephritis

In early stages the amyloid kidney usually presented a clinical picture almost indistinguishable from that of the nephrotic stage of glomerulonephritis A palpable liver or spleen is seldom observed at onset of these symptoms and correct diagnosis is suggested only by the fact that the syndrome is superimposed on chronic sepsis or tuberculosis Early diagnosis is important since the condition may clear up if the underlying disease can be radically treated otherwise renal failure and hypertension may develop

Lower Nephron Syndrome is discussed by G E Burch and C T Ray[2] (Tulane Univ) The general clinical pattern varies little with the responsible etiologic factors which include crushing injury wound abdominal operation burn blood transfusion reaction sulfonamide intoxication heat stroke malaria poisons hemolytic anemia uteroplacental damage eclamp ia acute pancreatitis and shock from various

(2) A n J t M d 31 759 772 ovembe 1949

causes A patient with lower nephron nephrosis resulting from a crushing injury or some other cause at first appears *to be in good condition but in a few hours he quickly passes* into the first phase of shock Injured areas become badly swollen and loss of fluid into tissue spaces results in hemo concentration Skin tends to be pale cold and moist although blood pressure generally remains almost normal apparently because of compensatory vasoconstriction When this vaso constriction is no longer maintained blood pressure falls rap idly a characteristic of the second phase of shock The mor tality rate is about 90 per cent once the cardinal signs of oliguria excretion of heme pigment azotemia and hyperten sion develop

The first or second samples of urine tested following an injury resulting in lower nephron nephrosis contain blood albumin creatine granular casts and pigment granules Spe cific gravity tends to become fixed at 1 010 Urine volume re mains low and may even approach anuria Urine is usually acidic It is brown because of acid hematin not because of the presence of erythrocytes The pigment usually shows a broad band in the red zone signifying a metmyoglobin compound as well as two bands in the yellow green portion closely re sembling those of oxyhemoglobin Excretion of pigment be gins to decrease in one or two days and casts appear in the urine in large quantities Amount of urine excreted decreases progressively

Blood studies show an accumulation of urea potassium and phosphate carbon dioxide combining power progressively falls and chloride tends to decrease probably because of in ability of tubules to reabsorb it The latter part of the first week is usually the critical period If the patient recovers there is sudden diuresis followed by a urinary output which gradually rises to abnormally high levels Cardiac irregulari ties may occur during the critical period electrocardiographic changes resembling those in potassium poisoning may be noted Though the potassium level may be greatly increased *it is not* known whether levels attained are sufficient to explain the electrocardiographic manifestations

Kidneys are usually swollen and increased in weight The outer surface is pale smooth and glistening and a clear or slightly bloody fluid oozes from the cut surface Cortex bulges

and is moist pale and in sharp contrast to the cyanotic appearing medulla Degeneration and necrosis involve the lower part of the nephrons inflammatory reactions develop in interstitial spaces occasionally thrombosis of and severe damage to adjacent veins occur and heme casts are found in lower portions of the tubules There are slight or no changes in upper parts of the nephrons If the patient survives 10 days degenerated tubular epithelium will probably be completely re epithelized

Although the exact mechanism for this syndrome is unknown certain facts have been established With destruction of muscle there is release of myoglobin When pigments are liberated in large quantities and cannot be metabolized in usual fashion by the liver to be excreted in bile they are excreted by the kidneys Mechanism by which pigments reach the lumen of the tubules is not clear Heme compounds are apparently concentrated or precipitated in the lower part of the nephron It has also been proposed that disturbances in renal blood flow particularly in the presence of shock are of paramount importance in diminishing renal function and in damaging the nephron Oliguria may develop because of a disturbance in glomerular filtration resulting from impairment of renal circulation tubular obstruction which interferes with rate of urinary flow or reabsorption of glomerular filtrate by damaged lower tubular portions of the nephron

If the patient has had an injury or a reaction which is known to produce lower nephron nephrosis enough fluids should be administered to maintain diuresis A large portion of the necessary fluids and carbohydrates should be given by gastric or duodenal tube Diet consisting of 150 Gm butter and 200 Gm sugar a total of 2 000 calories contains practically no protein and little potassium and phosphorus Contrary to most opinions severe to complete restriction of protein in the diet reduces protein catabolism to such low levels that after three days the daily nitrogen excretion is less than 6 Gm Alkali such as sodium bicarbonate should be given to maintain an alkaline urine Patients should be carefully watched for oliguria to avoid overloading with fluid Morphine should be given for pain and the patient should be comfortably warm but not overheated Local surgical treatment of injured areas should be carried out The role of sympa

thetic blocking or sympathectomy is still to be evaluated

Once renal failure with oliguria and progressive uremia develops relatively little can be done except for peritoneal lavage use of an artificial kidney or dialysis It is unlikely that decapsulation is of any value Peritoneal lavage is per formed by placing a catheter in an upper lateral abdominal quadrant and another in the lower contralateral abdominal quadrant and continuously running 18 24 L modified Tyrode s solution through the peritoneal cavity every 24 or 48 hours This solution has sulfadiazine heparin and penicillin added to prevent clotting and infection To remove fluid from the body the solution is made hypertonic by increasing the amount of glucose One type of artificial kidney consists of many dichotomous branching dialyzing tubes submerged in dialyzing fluid In another a large drum on which 40 45 yd of visking cellulose are wound in spiral fashion rotates pass ing the cellulose tubing through a tray of dialyzing fluid The patient s blood enters from an artery into one end and is re turned to a vein from the other end Recently gastric lavage has been advocated A special gastric tube preferably with two lumens irrigates the stomach with about 10 L of a spe cial fluid for 24 hours Rate of irrigation is about 150 drops/ minute Intestinal irrigation with saline has been carried out with a rubber tube a small balloon in its tip passed various distances down the intestinal tract

Lower Nephron Nephrosis Report of Treatment of 44 Patients by Repeated Replacement Transfusions J Dausset[3] (Paris) removed nonprotein nitrogen from the blood of anuric patients by removing large volumes of blood and re placing it with blood of donors as is done in infants with erythroblastosis fetalis Study of decrease in blood urea nitro gen level after replacement transfusion showed that replace ment with a quantity of blood equal to the total blood volume of the patient s body permitted maintenance of urea balance and replacement by a quantity equal to two times the blood volume of the patient permitted lowering of blood urea nitro gen by 33 per cent from beginning to end of the procedure and by 25 per cent the day after the procedure

Replacement transfusion was useful whatever the origin of lower nephron nephrosis but particularly so in failures due

(3) A ch I t Med 85 416-431 March 1950

to presence in the blood stream of nondialyzable heme pigment (as in transfusion incompatibilities massive hemolysis crush syndrome or burns) or of a poison linked with a non dialyzable protein Of Dausset s 44 patients 24 had anuria from hemolytic septicemia 3 from mercury poisoning 6 post operative anuria 3 postscarlatinal nephrosis 3 anuria from hepatonephrosis of undetermined origin and 1 each from sulfonamide nephrosis intoxication with sodium chlorate oliguria following severe burn transfusion reaction and anuria during blackwater fever

Large quantities of relatively fresh blood of a compatible type are needed for replacement transfusion but this disad vantage is lessened by use of type O blood and of Witebski substances in patients with blood of type A B or AB Trans fusion reactions were identical with those occurring after ordi nary transfusions Frequency of such reactions was multiplied by a great number of donors Possibility of transmission of the virus of homologous serum jaundice was a further danger

Of the 44 patients treated 29 recovered Failures were usu ally attributable to instituting treatment too late

Technic —Study of recipient s blood should include typing in Landsteiner system and the standard Rh system and systematic test ing for irregular agglutinins complete and incomplete and cross matching Bank blood was used it it had not been stored longer than a week but fresh blood stored 24 or 48 hours was preferred A half hour before the procedure patients were given 0 01 Gm mor phine sulfate and 1 5 Gm calcium gluconate was given during the procedure to prevent tetany from sodium citrate Injection of blood was done by the usual indirect transfusion using a large needle so that blood flowed freely If the venous network was well developed exsanguination was done through a second large needle coated with silicon or paraffin and introduced with the point heading distally into the largest vein available in the extremity opposite that used for transfu ion Heparin (2 mg /kg body weight) was given intravenously half at the beginning and half midway in the opera tion

When a catheter of polyvinyl was used in place of a metal needle only 1 mg heparin/kg or none was needed In using the catheter Dausset preferred to make an incision in the short saphenous vein on the femoral triangle level To upply force to insure an active outflow of blood a simple transfusion pump was useful

During the procedure intake and output of blood was exactly bal anced to avoid fluctuations exceeding 10 per cent of the patient s total blood volume Blood was exchanged at a rate of 500 cc every 5 10 minutes When exsanguination was discontinued injection of

blood equal to 10 per cent of blood volume of the body (500 cc in adults) was given in excess of the amount removed to compensate for dilution of injected blood Replacement transfusion may be done early and peritoneal dialysis then undertaken for 12 24 hours To avoid formation of adhesions in the peritoneum dialysis is then discontinued If urine output is not resumed and if poor condition of the patient persists a second and sometimes a third replacement *transfusion should be done*

Nephrotic Syndrome Natural History of Disease Lewis A Barness Gretchen H Moll and Charles A Janeway[4] reviewed records of 208 patients with the nephrotic syndrome seen in the Children s and Infants Hospitals of Boston from 1926 to 1948 Main criteria for differentiation of lipoid nephrosis (161 patients) and the nephrotic stage of chronic glomerulonephritis (47 patients) were hypertension or azotemia for longer than one month in patients with the latter disease which occurs more frequently in children over 4 Other features of the two diseases were often indistinguishable None theless it was thought desirable to differentiate between them since apparently few if any patients recover from the nephrotic syndrome if evidences of glomerulonephritis are clearcut

Lipoid nephrosis was characterized by insidious onset of edema in young children usually aged 1 4 Findings included edema hypoproteinemia hypercholesterolemia and heavy proteinuria Blood pressure was sometimes elevated for short periods but rarely over one month Microscopic hematuria did not exclude the diagnosis though macroscopic hematuria was usually evidence of glomerular involvement

Symptoms and findings in lipoid nephrosis often persisted one to three years without specific therapy Exacerbations with infection followed by remissions shortly after infection and remission soon after onset of the disease were relatively common Prognosis was not related to number or duration of exacerbations Deaths before 1942 were chiefly due to intercurrent infection After 1942 with advent of antibiotics death from infection became less common and usually occurred at home presumably because treatment was not promptly instituted Of the 161 patients with lipoid nephrosis 45 died In 23 of the 28 in whom cause of death was known death was due to infection In contrast of 19 children with

(4) P d t s 3 486-503 M h 1950

chronic glomerular nephritis in whom cause of death was known 12 died of uremia and only 5 died of infection

No form of treatment for lipoid nephrosis was wholly satisfactory Paracentesis transfusion and low salt diet were the most common supportive measures used Antibiotics were valuable during infections and apparently lowered mortality It is suggested that focal sources of infection be eliminated by operation only when surgery is definitely indicated Injections of salt poor concentrated human serum albumin and induction of measles are being evaluated as methods of inducing diuresis

There was no apparent constitutional defect in these children before onset of disease and growth and development were normal after recovery Approximately one half of the patients with clinical diagnosis of lipoid nephrosis apparently recovered completely without residual disease A small number showed persistent albuminuria or hypertension It is hoped that with closer supervision of patients and adequate chemotherapy *recovery figures can be significantly increased*

Chronic Nephritis and Nephrosis in Children is discussed by H H Boyle and H J Hebert on the basis of a study of all children admitted to Children s Memorial and St Luke s Hospitals Chicago with diagnosis of chronic nephritis or nephrosis between January 1946 and January 1949 a total of 59 cases Differentiation between chronic nephritis and nephrosis was always attempted and was usually possible after a few weeks observation Chief criteria for differentiation were the absence of hematuria azotemia and hypertension in nephrosis and their presence in chronic nephritis Most emphasis was placed on hematuria

Etiology of chronic nephritis and nephrosis in children is unknown Onset of both is usually insidious and acute febrile infection rarely precedes onset of edema Of the 59 patients studied only 9 had had acute infection within a month before onset of symptoms

Of the 22 deaths 5 were due to acute infection The remaining 17 apparently were due to complications arising directly from the primary kidney disease These figures are in sharp contrast to those quoted before widespread use of antibiotics when most patients died of acute infection In 10

(5) M Cl North Am 34 71 94 J y 1950

of the 13 seen at autopsy gross and microscopic changes characteristic of chronic glomerulonephritis were found in the remaining 3 anatomic findings agreed closely with Fahr s original description of genuine nephrosis

Early clinical findings in chronic nephritis and nephrosis are similar Age at onset varied from 1 to 13 years but only seven children were over 6 years at onset of symptoms Edema was the one outstanding symptom and dominated all others It was generalized at first later accumulated in serous cavities particularly the peritoneal cavity and finally tended to disappear Clinical condition differed decidedly in those with chronic nephritis and those with nephrosis in the third or drying up stage During this stage children with chronic nephritis were in increasingly poor condition with gradually diminishing kidney function Children with nephrosis gradually improved during the third stage and some eventually recovered completely

Differentiation between chronic nephritis and nephrosis was done first by laboratory findings rather than by clinical symptoms All but one patient with a diagnosis of chronic nephritis had blood in the urine None with the diagnosis of nephrosis had hematuria With nonprotein nitrogen elevation the criterion for dividing the two groups results were almost but not quite the same Seven children with chronic nephritis had nonprotein nitrogen levels below 35 mg/100 cc and eight of those with nephrosis had readings higher than 35 mg/100 cc In general hypertension with progressive kidney failure developed in children with chronic nephritis whereas those with nephrosis had no hypertension Kidney function as determined by ordinary function tests was impaired in chronic nephritis and not in nephrosis The authors routinely used two tests of kidney function Neither test is accurate if there is moderate or severe edema and urinary output is low because both depend on output Phenolsulfonphthalein was injected intravenously and the amount of dye excreted in 2 hours 15 minutes measured Normal kidneys excrete 80 85 per cent of the dye With progressive kidney damage of chronic nephritis excretion gradually goes down to zero A modified Mosenthal test was used to determine concentrating ability of kidneys A test period of 24 hours beginning at 7 00 a m was used The usual diet was given with 8 oz

fluid with each meal but no fluid between meals Two hour specimens were collected during the day and night urine was collected separately Normal kidneys excrete specimens with specific gravity ranging from 1 015 to 1 025 Damaged kidneys did not concentrate so highly as normal and the range was also less

General treatment consists of hygienic environment sufficient rest and adequate diet Children should be hospitalized early for diagnostic measures and regulation of diet Protracted hospitalization is not advised however A child if afebrile and able to walk around should not be kept in bed because of edema For the past 2½ years the authors have used the acid ash regimen in treating these patients The three essential features of this treatment are liberal fluid intake restriction of sodium chloride and acidification of body fluids with an acid ash diet ammonium chloride and hydrochloric acid Fluid intake of 1 500 2 000 cc is maintained Sodium chloride is restricted to 1 2 Gm daily Acid ash diet is essentially a low salt high protein diet with elimination of citrus fruit juices which are alkaline ash Ammonium chloride may be given as enteric coated tablets 5 gr three times daily at first then 10 gr three times daily Dilute hydrochloric acid 5 drops three times daily is given in water or lona lac* Edema may increase during the first 7 10 days of treatment before diuresis begins Treatment should be continued three weeks Results indicate that edema responds better to this regimen than to any other It is not a cure for nephrotic edema but patients are improved clinically Those who did not have prompt diuresis with treatment did mobilize fluid into the peritoneal cavity more rapidly than those not treated

Of the 43 children in this study with chronic nephritis 22 were alive at last observation Two had made a complete clinical recovery and 20 had evidence of active nephritis Of 16 *children with nephrosis 15 were alive* Three of these had completely recovered and 12 had evidence of nephrosis though 6 were free from edema and clinically well except for albuminuria The striking difference in mortality between the two groups (48 8 per cent for chronic nephritis and 6 25 per cent for nephrosis) and the corresponding difference in condition of those now alive is convincing evidence that differentiation between the conditions should be attempted

Electroencephalographic Findings in Acute Nephritis are reported by James G Hughes Fontaine S Hill and Billie Camp Davis[6] (Univ of Tennessee) In 24 children with acute nephritis 164 electroencephalograms were obtained Electro encephalographic abnormalities were noted in 22 of the 24 children

Chief changes were bursts of slow frequency waves of high microvoltage instability of EEG pattern and suppression of alpha activity with increase in fast frequencies of low am plitude Character of the EEG tended to vary from day to day and could not be correlated well with the clinical condi tion of the patient However when acute nephritis persisted there was increased likelihood of EEG abnormalities with brain potentials returning to normal as nephritis receded Whether persistent EEG abnormalities endure following acute nephritis was not determined No direct correlation between degree of hypertension and EEG abnormalities was found nor was there a clear relationship to edema anemia or azotemia

Of the 24 children with acute nephritis 22 showed abnor mal brain potentials but only 12 had symptoms referable to the nervous system These observations indicate that electro encephalography offers a sensitive approach to cortical dys function in acute nephritis

Diabetic Nephropathy Focal hyalinization in intercap illary connective tissue of the kidney in diabetes mellitus was described in 1936 by Kimmelstiel and Wilson They termed the lesion intercapillary glomerulosclerosis and related it to a clinical syndrome characterized in addition to diabetes mel litus by proteinuria widespread edema hypertension and eventual renal failure The clinical syndrome is not recognized as frequently as is the kidney lesion which suggests that the glomerular changes do not always result in nephrotic hyper tension

To clarify certain questions with regard to this disease process Eugene I Zins[7] (Metropolitan Hosp New York City) reviewed 50 consecutive autopsies of diabetic men and women Controls used in estimation of histologic lesions were 50 nondiabetics of a corresponding age group with kidney in

(6) J Ped t 36 451 459 Ap 1 1950
(7) Am J M Sc 218 408 418 Oct be 1949

volvement such as benign nephrosclerosis chronic glomerulo nephritis and chronic pyelonephritis

The typical lesion of intercapillary glomerulosclerosis consists of spherical dense hyalinized material between the glomerular tufts which appear homogeneous under low power All degrees of involvement may be found in one glomerulus In sections showing the lesions many glomeruli show evidence of fibrosis a lesser involvement which may progress to the typical spherical lesion In Zins s study fibrosis of the glomerulus was classified as the minimal lesion of intercapillary glomerulosclerosis Glomeruli containing occasional spherical hyalinized lesions were listed as moderately involved The lesion was considered advanced when hyalinization existed in all glomeruli

In this series glomerular disease was discovered in 82 per cent of diabetics Previous studies have placed incidence between 20 5 and 63 5 per cent Increasing recognition of the stage of fibrosis by many investigators explains the increased incidence in recent studies The control group studied affirms previous conclusions that moderate or advanced intercapillary glomerulosclerosis is rare in the absence of diabetes Only one instance was found among the 50 controls this in a woman aged 63 who died on admission Since blood sugar and urinary sugar determinations were not made possibility of diabetes cannot be excluded This case may be similar to others reported of nondiabetics who have evidence of the hyaline change of intercapillary glomerulosclerosis The minimal lesion was indistinguishable from many lesions found in nondiabetics and therefore no accurate estimate of its specificity can be made

Comparison of incidence of intercapillary glomerulosclerosis with known duration of diabetes mellitus revealed that in the group having diabetes over 15 years all had the renal complication It was not possible to relate hypertension proteinuria the nephrotic syndrome and renal failure to the degree of involvement of the kidney except in the few in whom the lesion was far advanced In the latter instance the components were usually found to make clinical diagnosis of intercapillary glomerulosclerosis obvious Before the advanced stage is reached it is only possible to speculate on the amount of focal hyaline change that is taking place It is

reasonable to assume however that the renal lesion will progress despite therapy With increase in life expectancy for controlled diabetics more awareness of the pathogenesis and pathology of this complication is needed

Necrosis of Renal Papillae is a striking pathologic lesion found at autopsy in 25 per cent of diabetic patients with acute pyelonephritis and in 2 per cent of nondiabetics with this dis ease Acute pyelonephritis occurs in 12 20 per cent of dia betics and in 3 3 per cent of nondiabetics Most nondiabetics who have papillary necrosis without pyelonephritis have uri nary tract obstruction

Edward D Robbins (Chicago) and Alfred Angrist[8] (Long Island N Y) describe 14 cases of papillary necrosis ob served at Queens General Hospital which included 13 acute cases and 1 in which healing occurred 8 being in diabetics and 6 in nondiabetics The eight diabetic patients were younger as a group (average age 57) and had a shorter clini cal course than the nondiabetics On admission two were in coma and one was stuporous Two others had glycosuria of 3-4+ but urine contained no acetone however both were thought to be in diabetic coma Striking azotemia and mod erate anemia were present in all patients in whom determina tions of blood urea level and red cell count were made Three patients died shortly after admission and the others within two months However necrosis of renal papillae is not in variably fatal as evidenced by the healing which had occurred in one patient The six nondiabetics were all over age 73 five were men with prostatism and/or urinary tract infection The average hospital stay before death was two months

Experimentally necrosis of renal papillae has been pro duced by specific chemical poisons and by fat free diets which appear to be deficient primarily in certain long chain unsatu rated fatty acids Therefore it is possible that a parallelism may exist between disturbed fat metabolism in diabetics in nondiabetics with urinary tract obstruction and sepsis and in experimental animals with fatty acid deficiency It is also pos sible that papillary necrosis may be the homologue of cortical necrosis of the kidney on the basis of altered hemodynamics with spasm of medullary vessels rather than cortical vascu lature as the significant factor in the mechanism

(8) A I t M d. 31 773 93 N mbe 1949

Effect of Febrile Plasma, Typhoid Vaccine and Nitrogen Mustard on Renal Manifestations of Human Glomerulonephritis It is generally thought that remissions in the nephrotic stage of glomerulonephritis may be caused by intercurrent infection Because the febrile phase of infection may be accompanied by profound disturbance in renal hemodynamics it seems possible that both decrease in proteinuria and diuresis may be directly attributable to alteration in renal hemodynamics It has been reported that administration of one of the nitrogen mustards (HN_2) prevents development of the Shwartzman phenomenon in rabbits Because diffuse glomerulonephritis may be the result of immunologic alteration in renal tissue it seems conceivable that a common factor may be operative in infection and following administration of febrile plasma typhoid vaccine or HN Hence reactive factors may be present in plasma of patients with acute infections which produce remission of the nephrotic syndrome

To test these possibilities Herbert Chasis William Goldring and David S Baldwin[9] (New York Univ) explored effects of (1) pyrogenic reaction (2) infusion of plasma from patients acutely ill with pneumococcic and hemolytic streptococcic infections and (3) nitrogen mustard on protein excretion diuresis and rate of glomerular filtration in patients with diffuse glomerulonephritis In four patients daily weight 24 hour urinary volume and urinary protein excretion rate of glomerular filtration and renal plasma flow were observed

In one patient on two occasions the pyrogenic reaction induced with typhoid vaccine resulted in a decided decrease in proteinuria accompanied by decreased filtration rate the one time it was measured No diuresis occurred It seemed that the decrease in proteinuria was related to renal hemodynamic alteration manifested in part by decrease in filtration rate Two patients given plasma showed no decrease in proteinuria or diuresis Nitrogen mustard was administered intravenously to three patients proteinuria decreased in all and diuresis occurred in one

These observations indicate that reversal of renal manifestations of glomerulonephritis in man can be induced by administration of HN_2

(9) Proc. Soc. Exp. Biol. & Med. 71 565 567 August, 1949

Influence of Dietary Protein on Function of Diseased Kidneys was studied by Hans Olaf Bang[1] (Kommunehospitalet Copenhagen) in 11 patients with glomerulonephritis or pyelonephritis Disease was stationary in nearly all cases so that variations in clearance of urea inulin and diodrast® following changes in protein content of diet could not be attributed to improvement or exacerbation of the renal lesion In most cases clearance values were determined first after a high protein diet and next after a low protein diet At least one week elapsed between change of diet and clearance experiment

In nine patients urea clearance was lower on the low protein diet than on high protein diet (average fall 28 7 per cent of values on a high protein diet) Also inulin clearance values generally fell almost paralleling those of urea clearance (average fall 22 7 per cent) Diodrast® clearance on the other hand was not lowered significantly The two patients with poorest renal function both responded inversely to change in protein intake In both cases urea clearance and in one also inulin clearance and diodrast® clearance were lowest on the high protein diet At the same time the patients general condition seemed better on the low protein diet than on the one rich in protein

In estimating renal function by clearance determinations in patients with renal lesions it is necessary to take into account protein content of diet when using urea clearance and inulin clearance

Carbon Tetrachloride Poisoning in Man Mechanisms of Renal Failure and Recovery Jonas H Sirota (New York City) states that carbon tetrachloride poisoning whether by inhalation or ingestion is often associated with damage to the distal kidney tubules This type of acute renal failure has therefore been included among the subclassifications of lower nephron nephrosis

By means of the Fick principle renal plasma flow was determined in four patients with acute carbon tetrachloride poisoning Renal venous blood was obtained by catheterization of the right renal vein Para aminohippurate (PAH) was used as the test substance In two patients renal plasma flow and PAH renal extraction ratio were decidedly reduced in

(1) Acta med Scand nav (pp 234) 136 18 21 1949
(2) J Clin. Investig t on 28 1412 1422 N mbe 1949

one they were normal on the 24th day and in one who had had oliguria for 17 days renal plasma flow was 592 cc/minute on the 37th day and PAH extraction ratio continued to be depressed

It is concluded that oliguria and anuria of carbon tetrachloride poisoning and strikingly depressed renal clearances of all substances during early diuresis are the results of decided reduction in renal blood flow and glomerular filtration as well as abnormal tubular back diffusion of filtrate It is assumed that back diffusion plays the most important role during early oliguria as decreased renal blood flow does during late oliguria and early diuresis

Recovery of renal function after acute renal failure due to carbon tetrachloride poisoning is characterized by three clinical phases The first phase starts with cessation of oliguria and is associated with rising plasma creatinine and urea concentrations despite adequate urine flow It lasts from one to three days The second starts with a rapid decline in plasma urea and creatinine levels The third starting about the 40th day is characterized by gradual improvement in renal blood flow and glomerular filtration so that the lower limit of normal is reached 100 200 days after poisoning

Renal Hematuria and Hypoprothrombinemia With advances in urologic knowledge diagnosis of essential hematuria is less prevalent and fewer normal kidneys are being removed Still smaller numbers may reach the pathologist when urologists recognize that such hematuria may be due to hypoprothrombinemia C Balcom Moore[3] (Walla Walla Wash) became interested in this subject after seeing two patients with unilateral hematuria associated with low prothrombin blood levels In neither patient could any cause for hypoprothrombinemia be found nor could any definite personal or family history of bleeding be elicited However variations in liver size and tenderness in one patient and a gallstone in the other may have signified some failure in synthesis of prothrombin due to liver disease although results were normal in the one patient given liver function tests

In recent years there have been many case reports of hematuria due to dicumarol* or heparin therapy However there are only rare reports of hematuria as the first symptom

of hypoprothrombinemia from other causes In 7 of the 14 case reports of idiopathic hypoprothrombinemia found in the literature hematuria was stated to have been present at some time In 6 of the 14 vitamin K or blood transfusions failed to give any consistent benefit In four vitamin K produced cure Hematuria was a prominent symptom in one the presenting complaint in another and the only symptom of prothrombin deficiency as in Moore s two cases in a third In contrast the reduced prothrombin level was apparently congenital in four other cases it was improved by blood transfusions but was unaffected by vitamin K Hematuria was present in two

Moore emphasizes that any patient with obscure hematuria should have a blood study including prothrombin and clotting times as part of the urologic investigation Blood dyscrasias particularly prothrombin deficiency are probably often overlooked as a cause for unilateral renal hematuria

Clinical Study of New Sulfonamide (NU-445) in Treatment of Urinary Tract Infections Joseph A Lazarus and Lewis H Schwarz[4] (New York City) studied the effectiveness of 3 4 dimethyl 5 sulfanilamide isoxazole (NU-445) in 25 patients with urinary tract infections caused by Aerobacter aerogenes Bacillus pyocyaneus Escherichia coli Proteus morganii Proteus vulgaris Staphylococcus aureus and Streptococcus hemolyticus Eighteen had unmixed and 7 mixed infections There was a total of 33 infections most of which were due to B pyocyaneus or Esch coli

NU-445 was administered orally to all patients and in addition eight were treated with bladder instillations Daily oral dose varied from 4 to 16 Gm and average duration of treatment was 25 days One patient received as much as 1 680 Gm over 140 days but average total intake was 259 Gm

Infecting organisms were eradicated in 20 instances (60 6 per cent) NU-445 was ineffective in 10 (30 3 per cent) and results in the remaining 3 were equivocal A remarkably high incidence of positive responses to treatment with NU-445 occurred in patients with B pyocyaneus and Esch coli infections The drug proved effective in cases in which sulfadiazine and/or streptomycin had failed to eradicate the pathogens

Solubility of NU-445 obviated the need for concomitant

(4) J Urol. 61 649 657 March, 1949

alkali medication even when large doses were administered In none of the patients was crystalluria or hematuria ob served Similarly there was no evidence of deposition of crys tals in the urinary tract In general NU 445 was tolerated without serious complications however treatment was dis continued in two instances because of untoward effects Uri nary excretion studies showed prompt elimination of NU 445

It is concluded that NU 445 is a valuable adjuvant in treatment of urinary tract infections caused by B pyocyaneus and Esch coli

Oral Administration of Aureomycin in Treatment of Urinary Infections is reported by Alexander M Rutenburg and Fritz B Schweinburg[5] (Boston) Aureomycin 2 Gm orally was given daily in divided doses for four to six days or longer to an unselected group of 26 patients with acute and chronic urinary infections including 5 with chronic renal in sufficiency Seventeen had been treated with other antibiotics without clinical or bacteriologic improvement Twenty had one or more of the following complications hydronephrosis calculi ureteral stricture and prostatic obstruction Twenty one of the infections were due to a single organism and five to more than one Organisms involved were Escherichia coli (8 cases) Aerobacter aerogenes (12 cases) Pseudomonas aeru ginosa (11 cases) Proteus vulgaris (1 case) hemolytic Staphylococcus aureus (1 case) and Streptococcus faecalis (1 case)

Sixteen patients were promptly cured by a single course of oral aureomycin Severa courses were required for the three patients who had recurrent infection In these and in one pa tient with a vesicovaginal fistula the underlying disease had not been dealt with successfully All the patients in this series had clinical improvement even the seven in whom bacteria was not eradicated (in one Esch coli and in six Ps aeruginosa) There was exact correlation between bacterial sensitivity in vitro and immediate bacteriologic response re gardless of whether the complicating disease was dealt with successfully In the latter cases recurrence or reinfections were to be expected and in fact occurred Such patients can not be permanently cured by any antibiotic In no case did bacterial resistance to the drug develop during treatment

Aureomycin orally was as effective as previous administration of the drug intramuscularly in another series of patients

Conservative Treatment of Anuric Uremia In a case of anuria G M Bull A M Joekes and K G Lowe[6] (London) recommend that the physician first exclude obstruction distal to the renal pelvis and factors outside the kidney such as general circulatory disturbances and alkalosis which may produce renal failure All others are treated along the lines to be indicated Unless terminal nephritis or nephrosclerosis is the cause of anuria recovery may occur Reversible causes of anuria include lower nephron nephrosis from mismatched blood transfusion crush syndrome intravascular hemolysis from various causes postabortion anuria and the lesion following protracted shock toxic nephrosis from poisoning by mercury carbon tetrachloride phenol etc and acute nephritis

TREATMENT —To prevent waterlogging which is common fluid intake is limited to the amount of water usually lost by routes other than the kidney (about 1 L) Because there is no pathway for electrolyte excretion other than the kidney diet is electrolyte free until diuresis starts While the patient is still anuric no attempt is made to correct the electrolyte disturbances since administration of potassium may cause sudden death from cardiac arrest and excess of sodium is probably harmful in other ways Because end products of protein metabolism other than urea are possibly toxic it is desirable to depress nitrogen metabolism as much as possible Since nausea is common in anuric patients they are fed through a permanently indwelling stomach tube and are given 400 Gm glucose and 100 Gm fat daily This 2 500 calorie protein free and mineral free diet can be taken with little discomfort for periods up to three weeks On admission a stomach tube is passed through the nose Through this tube a mixture of the following ingredients is permitted to drip at a steady rate 24 hours a day 400 Gm gluco e 100 Gm peanut oil sufficient acacia to emulsify up to 1 L water and vitamins if desired All vomit is collected filtered through lint and returned to the stomach in the same way Drip feeding should be di continued and superseded by a low protein diet when urine output exceeds 1 L daily Because anemia is known to lead to diminished renal function fresh packed red cells are transfused if the hemoglobin concentration is below 70 per cent

The effects of this regimen were studied on control patients with no evidence of renal disease patients with reduced renal function but without anuria and patients with anuric uremia In the five controls this regimen resulted in rapid reduction of endogenous nitrogen metabolism as indicated by a

(6) L et 2 229 34 A g 6 1949

steady diminution of urea nitrogen excretion Eleven patients with extreme oliguria or anuria lasting 7 21 days were treated 4 died Of the four who died two were comatose when admitted One was admitted on the eighth day of anuria having had a laparotomy and splanchnic block the previous day On the next day pneumonia developed and the abdominal wound burst open he died of these complications The fourth patient died after diuresis began probably from a cerebral abscess In no instance did extreme oliguria or anuria last for less than 7 days and one patient did not achieve an effective urinary output for 24 days Seven patients not only survived but left the hospital free from symptoms and with adequate renal function In all there was a considerable slowing of the rate of rise of blood urea level after treatment began After the same duration of anuria or at the same level of blood urea these patients were in much better general condition than previous patients who had not been on the regimen

This regimen is recommended for patients first seen early in anuria and not already waterlogged Dialysis methods because of their dangers and difficulties should be used only for patients with gross water mineral and nitrogen imbalance

Treatment of Uremia with Intestinal Dialysis is discussed by C Brun (Copenhagen) The principle of intestinal dialysis is that the lumen of portions of the intestine is irrigated with suitable solutions so that noxious retention products which cannot be excreted by the kidneys pass by diffusion into irrigation fluid and are removed with it from the organism What is accomplished is a substitute for filtration

It is not known which substances produce symptoms of uremia and therefore should be removed Electrolytic disturbances play a considerable role and urea plays little primary part in development of uremic symptoms It is supposed that retention of substances such as phenols and guanidine plays a certain part perhaps in conjunction with phosphates It is now generally assumed that uremia is an intoxication from many different substances about which relatively little is known This is of great importance when effectiveness of treatment with dialysis is evaluated because analytic methods generally used are of little value

Water equilibrium in the course of intestinal dialysis can

(7) S a J Cl & L b J t g t 1 328 333 1949

be controlled in such a manner that great changes can be avoided or if desired considerable edema removed By varying the content of sodium and potassium chlorine and bicarbonate in irrigation fluid and in liquids given parenterally electrolyte composition of the organism can be arbitrarily changed—the concentration of ions can be increased or decreased Urea passes readily by diffusion through intestinal mucous membrane and therefore can be removed from the organism by intestinal dialysis With the exception of urea and nonprotein nitrogen there is a rise in concentration of all other retention products that have been determined

It is difficult to assess clinical effects of dialysis Though it has seemed of value in some cases beneficial effects may have been due to simultaneous blood transfusions or corrections of electrolyte imbalances Some recently reported observations seem to show that if patients are not overloaded with water and electrolytes and at the same time the energy requirements are met by means of fat and carbohydrates it is possible in anuria to obtain just as long and even longer periods of survival than are obtained with dialysis The treatment now generally recommended for acute uremia must be the high caloric regimen poor in liquid electrolytes and nitrogen If promising results of conservative treatment hold the scope of indication for active dialysis will undoubtedly be restricted Though it cannot yet be decided whether intestinal dialysis is effective investigations should be continued

Peritoneal Irrigation in Treatment of Acute Renal Failure It was demonstrated recently that patients dying of acute renal failure due to causes such as crush syndrome abruptio placentae toxemias of pregnancy transfusion reaction burn and heat stroke all show the same kidney lesion The distal segments of kidney tubules are involved and lesions vary from focal degeneration to necrosis and disintegration of epithelium This picture has been called lower nephron nephrosis Shock appears early and is easily treated but is followed by renal insufficiency George J Strean[8] (Jewish Gen l Hosp Montreal) successfully used peritoneal irrigation in a case

Woman 25 was hospitalized with a diagnosis of thrombasthenic purpura complicating pregnancy Her blood group was A Rh negative Transfusion with 500 cc whole blood was followed

(8) Am J Ob t & Gy 59 48 489 M h 1950

immediately by a severe chill and temperature rise. Although the donor s blood was first reported as Rh negative rechecking showed it to be Rh positive. The patient went into labor and 11 hours after admission delivered a dead 7 month fetus Catheterization at delivery yielded only 2 oz bloody urine Oliguria continued urine was bloody with many granular casts and for three days despite diaphoresis hot poultices to the loins intravenous glucose ureteral catheterization and lavage of kidney pelves oliguria became more pronounced and azotemia progressed

Peritoneal irrigation was instituted The solution was run in by gravity from large flasks through a Y tube into a drip bulb through a Berkefeld filter into a U tube over a water bath at 42 C and finally into the peritoneal cavity Sump drains were inserted into each flank the inlet tube pointing toward the mesentery the outlet tube into the pouch of Douglas The latter was connected to a large graduated jar to which a suction pump was attached Maximal blood clearance was found when the rate of flow was about 60 cc /minute Composition of the irrigating fluid was varied according to demands of the patient s electrolyte balance Other supportive therapy was also used

Urinary output increased rapidly after institution of peritoneal irrigation doubling in 24 hours Abnormal urinary findings disappeared rapidly but specific gravity remained low The tubes were removed on the eleventh day A few hours before their removal the patient had a generalized convulsion which recurred despite calcium gluconate and phenobarbital therapy Because of the possibility that seizures were caused by an electrolyte shift between extra and intracellular fluids due to loss of extracellular sodium in the irrigating fluid normal saline was given intravenously with dramatic results Later when this therapy was discontinued for 36 hours seizures recurred but were again controlled promptly with saline

The patient was discharged about a month after admission and four months later urinary findings were normal with a specific gravity of 1 033 Eighteen months later when laparotomy for a large ovarian cyst was done the peritoneal cavity was found to be free from adhesions

Peritoneal irrigation in renal failure can be successful only when pathologic changes are reversible If the renal lesion is permanent one can only prolong life for a short while but if the damage is such that sufficient functioning tissue will regenerate if given time it is possible to control azotemia temporarily so that adequate kidney function can be established

Nephrotoxic Nephritis in Rats Evidence for Glomerular Origin of Kidney Antigen David H Solomon Joseph W Gardella Herbert Fanger Frances M Dethier and Joseph W Ferrebee[9] produced nephrotoxic nephritis in rats by intra

(9) J E p M d 90 267 272 S pt mbe 1949

venous injection of rabbit anti rat kidney serum Rabbits were immunized by repeated intraperitoneal injections of blood free rat kidney suspensions Pools of rabbit anti rat kidney serums were partially freed of nonantibody protein by precipitation of a gamma globulin containing fraction this fraction was redissolved in saline and used as a nephrotoxic solution in place of whole serum A method for the crude separation of kidney into glomerular and tubular portions was devised and the separate portions were tested for their ability *to adsorb nephrotoxin from the gamma globulin containing* fraction of nephrotoxic rabbit serum

Acute nephritis when severe was characterized by heavy proteinuria edema ascites pleural effusion diarrhea anorexia emaciation elevation of blood urea nitrogen and pallor Histologic abnormalities were noted consistently only in animals which had shown severe acute nephritis while alive In these animals thickening of the basement membrane of the glomerular capillaries was the most frequent finding The membrane appeared to be widened by a combination of edema and tissue proliferation These changes were found in 35 of 45 severely nephritic rats Less frequently glomeruli exhibited increased cellularity and mild polymorphonuclear infiltration of the tuft exudation of albuminous fluid into the capsular space or early crescentic formation Colloid droplets were occasionally seen in the epithelium of proximal convoluted tubules Coagulated albuminous fluid and granular debris were frequently found in the tubular lumen Arteries and interstitial tissues were invariably normal

Adsorption with glomerular tissue was consistently effective in rendering the immune serum fractions no longer nephrotoxic As a rule 0 05 cc packed finely ground glomeruli was sufficient to remove an amount of nephrotoxin equivalent to that required for production of severe nephritis in one *rat* It is concluded that nephrotoxic serums of this type react primarily with glomerular tissue and by inference that the antigen essential for production of these antikidney serums is of glomerular origin

Effect of Protein Deficient Diet on Rat Kidneys was studied by *R Eker*[1] (Norwegian Radium Hosp Oslo) Rats were given a protein free basic diet of adequate caloric content with

(1) S and a J Cl n & Lab I e t g t 62 71 19 0

supplemental milk casein in desired amounts as the source of protein The kidneys were studied histologically and renal circulation was studied by injections of India ink

Necrosis and calcification starting in the ascending loop of Henle and dilatation of the tubules were observed in rats on protein deficient diets with 140 240 and 420 mg casein/100 Gm body weight/day Circulatory disturbances in the kidneys similar to those described as characteristic of the crush syndrome were found Both morphologic and functional changes observed in these experiments were related to those described as characteristic for lower nephron nephrosis

Involvement of the lower part of the nephron is comparatively rare Apparently the pathogenesis of such involvement is widely different It is not very probable that tubular damage is due primarily to circulatory changes since involvement is limited to the distal tubules That the lesions are due to some toxic metabolite which is reabsorbed or excreted in the distal tubule seems reasonable

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(1) Scand J Clin & Lab Invest 2 62 71 1950

The Digestive System



GEORGE B EUSTERMAN MD

PART V

THE DIGESTIVE SYSTEM

DISEASES OF THE DIGESTIVE SYSTEM 1940 50

Undoubtedly greater medical progress has been made in the past half century than in the previous 200 years Even in the past decade its momentum has not been greatly slowed despite deterrent factors inseparable from a global war Many diagnostic technics *and therapeutic procedures that had their inception in* the latter years of the previous decade came to fruition in whole or large part in recent years Significant as these innovations *are with respect to the digestive system they are overshadowed* by one of the greatest of medical discoveries the antibiotics the outstanding achievement of the decade under consideration

The Esophagus

Diaphragmatic hernia—Partial thoracic stomach (hiatal hernia) due to herniation of the upper part of the stomach through the esophageal hiatus of the diaphragm is more common than is generally realized Such possibility should be excluded in every middle aged dyspeptic in the absence of demonstrable disease in the upper part of the digestive tract or in the biliary and pancreatic system A little more than 90 per cent of patients with hiatal hernia seen in the larger medical centers were over 40 The various types of diaphragmatic hernia acquired after birth have been classified by Harrington (1948) who pointed out that esophageal hiatal hernia represents at least 95 per cent of the cases

Symptoms arising from the hernia per se are of wide variety and degree and many authorities believe there is no characteristic syndrome However Chester Jones (1941) expressed the belief that small hiatal hernias which constitute approximately 75 per cent of all hernias have a reasonably characteristic set of symptoms which under observation can be properly diagnosed Associated disease of the gallbladder or of the stomach and duo

tient with chronic recurring otherwise unexplainable, dyspepsia.

Peptic ulcer—The *genesis* of ulcer is still elusive. Current emphasis is on the psychosomatic factor and on corrosion from acid gastric juice The psychosomatic aspect has been so much in the foreground that many physicians and laymen have come to consider the neuropsychic factor as causative of disease particularly duodenal ulcer and chronic ulcerative colitis Those disagreeing with such a concept maintain that its proponents confuse a phase of the disease with its cause although they do not minimize the importance of treatment of this phase. Proof of psychogenesis is extremely difficult However much experimental and clinical evidence points to the psychosomatic nature of cardiospasm spastic or irritable colon and obviously the persistent vomiting and malnutrition which characterize anorexia nervosa

Hay Varco Code and Wangensteen (1942) produced gastric ulcer in dogs by intramuscular injection of histamine in beeswax which prolongs maximal secretion of hydrochloric acid Thus additional testimony to the great importance of acid in the genesis of ulcer was obtained Acute and subacute gastric ulcers were initiated in cats by Ivy and Roth (1944) who used caffeine in a mixture of beeswax and mineral oil

Investigations by Levin Kirsner Palmer and Butler (1948) confirmed those of Dragstedt and earlier workers that the volume of gastric secretion at night was usually highest in patients with duodenal ulcer In patients with gastric ulcer the average nocturnal volume of gastric juice was about the same as for normal subjects but the average content of hydrochloric acid was lower

Rivers and Roodenburg (1944) have shown that *radiation of pain* characterizes many penetrating or perforating ulcers Rivers (1947) description of the syndrome of peptic ulcer perforating to the pancreas is particularly enlightening

Among recent innovations in *treatment* are antacids like aluminum hydroxide in colloidal form which are not absorbed systemically and therefore do not predispose to alkalosis protein hydrolysates ion exchange resins continuous intragastric drip the psychosomatic approach and vagotomy The neutralizing or buffering effect of the various antacids singly or in combination has been the subject of numerous investigations both in vitro and in vivo by electrometric methods Adequate sus

denum is not uncommon and may be the basis of the digestive disorder The severity of the hernial symptoms is definitely related to associated complications particularly traumatic ulcer and incarceration of the stomach The diagnosis of diaphragmatic hernia broadly speaking, is essentially a roentgenologic problem Although the results of surgical repair are excellent as a rule current practice is to treat medically the uncomplicated small and medium sized hernias

Esophagitis stricture and ulcer—Esophagitis and its sequelae and esophageal ulcer like hiatal hernia with which condition these lesions are frequently associated are assuming increasing importance Wangensteen and Leven (1949) have advocated gastric resection for esophagitis or stricture or both of acid peptic origin

Esophageal varices with special reference to treatment—It has been estimated that 25 per cent of patients with hepatic cirrhosis and almost all patients with Banti s disease ultimately die of hemorrhage from esophageal varices Although splenectomy injection of sclerosing substances into the varices local application of oxidized cellulose (Oxycel) intraesophageal tamponade and thrombin therapy frequently control the bleeding the ultimate results have not been satisfactory as a rule Hence the advocacy of more direct procedures such as splenorenal or portacaval shunting operations by A O Whipple (1945) and Blakemore (1948) The most direct method of management is that of Phemister and Humphreys (1947) who carried out transthoracic esophagogastric resection after splenectomy and obliteration of the varices by injection had failed to control the tendency to hemorrhage Published reports of the end results are not too reassuring

The Stomach and Duodenum

Gastritis—There are many contradictory opinions regarding the degree to which gastritis may produce symptoms and its relation to other diseases specifically ulcer and carcinoma In our experience at the Mayo Clinic and that of many other clinicians and gastroscopists hypertrophic erosive or ulcerative gastritis is one of the most important clinical types because of its simulation of peptic ulcer and because it is a source of hemorrhage or both Whatever the conviction with respect to gastritis it is wise to carry out a gastroscopic examination in every pa

jejunal ulcer following gastroenterostomy if take down of the gastroenteric stoma and gastric resection is too hazardous and last but by no means least for gastrojejunal ulceration after adequate gastric resection

Hematemesis and melena —This dramatic frequently worri some and sometimes fatal aspect of peptic ulcer holds the sus tained interest of the profession Real progress in better under standing has been made in estimation of blood loss immediate and remote prognosis factors of risk role of diet and trans fusions and indications for surgery Details concerning these fea tures are contained in the 1948 and 1949 YEAR BOOKS OF MEDI CINE

Gastric carcinoma —Attempts at earlier detection of this dread disease one of the most pressing and difficult problems confronting the medical profession are characterized by two in novations routine roentgen examination of the stomach of ap parently normal individuals and cytologic study of the gastric secretions It is doubtful whether mass screening tests will prove practicable owing to the paucity of findings However repeated examination is indicated for patients with gastric ulcer gastric polyp and atrophy of the gastric mucosa Achlorhydric patients with gastric disturbances also deserve close surveillance A reli able biologic test for cancer promises to be the ultimate solution Papanicolaou reported his investigations on cytologic diagnosis in 1946 Subsequent observations have been made by Papanico laou and Cooper (1947) Fremont Smith Graham Ruth and Meigs (1948) Graham Ulfelder and Green (1948) Anderson McDonald and Olson (1949) and Lois Platt (1949) Despite some inherent difficulties it appears that cytologic examination may prove to be of real value in the early diagnosis of gastric carcinoma

Unfamiliar gastroduodenal lesions —Unfamiliar presumably rare lesions are usually not of great concern to the rank and file of physicians However such rarity often is more apparent than real Once physicians are aware of their existence it is surprising how frequently such lesions come to light to the credit of the physician and to the benefit of the patients Three types of dis orders that command consideration are (1) hemorrhagic gastro jejunitis following gastroenterostomy in infancy for congenital pyloric stenosis (2) nonspecific granulomatous inflammation of the stomach and duodenum and (3) prolapse of gastric mucosa

tained neutralization of the acid already secreted is not possible by routine methods Recent attempts have been made to prevent acid secretion by use of drugs with atropine like effect The most promising according to Longino Grimson Chittum and Metcalf (1950) is banthine an orally effective parasympatholytic Cummins Grossman and Ivy (1946) studied the time of healing of 69 duodenal and gastric ulcers with craters The average for the former was 37 days with a range of 16 68 days for the latter (six cases) it was 42 days with a range of 16-68 days

The ultimate results of medical treatment have been reported both here and abroad The reports of Kraup (*1946*) of Copenhagen Martin and Lewis (1949) of Cambridge England Raimondi and Collen (1946) and Flood (1948) are not encouraging Martin and Lewis (1949) in a study based on 10 years observation concluded that medical treatment did not influence the natural course of the disease and urged gastrectomy for all patients with peptic ulcer of 10 or more years duration preferably before age 50

The prevention of recurrences of peptic ulcer has been greatly stressed by several American authorities Althausen (1949) for example is convinced that the problem of peptic ulcer could be greatly lessened thereby He believes the most important known causes of recurrence of ulcer are physical and mental fatigue emotional disturbances dietary indiscretions and infections

Undoubtedly the most important development *during the* past decade from the gastroenterologic standpoint was bilateral *vagotomy* for peptic ulcer as conceived by Dragstedt and his associates in 1944 Since he published his clinical results and his illuminating experimental and physiologic investigations many reports of others have become available Proper appraisal of vagotomy has been difficult because of the claims of enthusiastic proponents on the one hand and of outspoken opponents on *the other*

To the impartial observer vagotomy would seem to have its greatest usefulness in combination with gastroenterostomy for duodenal ulcer when anatomicopathologic conditions do not permit gastric resection without undue risk in combination with gastroenterostomy for duodenal ulcer in the hands of the less expert surgeon especially in the unstable patient with hypersecretion and high concentration of hydrochloric acid for gastro-

Needle biopsy of the liver —Contributions by numerous au thorities at home and abroad attest the expediency and safety of needle biopsy even when the intercostal approach is used The results of needle biopsy and of studies of hepatic function by no means always parallel each other Nevertheless such combined procedure plus thorough clinical study represents distinct prog ress in the diagnosis and treatment of hepatobiliary disease

Treatment of hepatic amebiasis with chloroquine —N J Conan Jr (1949) reported the successful treatment of seven patients with chloroquine It undoubtedly is effective and tox icity is minimal An intestinal amebacide should be used in con junction with it

Acute pancreatitis —It is to be remembered that much of what is regarded as new in the knowledge of disease processes is a confirmation of long established facts this applies to pan creatitis as it does to other disorders However modern diag nostic and therapeutic technics permit clearer orientation as to incidence classification biochemical changes complications and treatment Elman s classification into pancreatic edema and pan creatic necrosis of the acute form in which the former predomi nates justifies conservatism Determination of the levels of serum and urinary amylase especially the former while symp toms are still active is essential to diagnosis Moderate elevation of serum amylase may also occur in acute biliary disease duo denal ulcer with involvement of the sphincter of Oddi acute perforating ulcer with perforative peritonitis and pancreatic car cinoma

Because of the current world wide attitude of therapeutic conservatism many articles on treatment have appeared in the past 10 years These differ in many respects although in princi ple the treatment is symptomatic and supportive in the main Differentiation of the acute edematous and the necrotic form or the ability to detect the transition of the former to the latter may be difficult Elman (1949) like many other surgeons has favored surgical intervention in the latter It has been his im pression that acute pancreatic necrosis can be diagnosed in nearly all cases but that it must be done purely on a bedside basis

Chronic relapsing pancreatitis —The classic report by Com fort Gambill and Baggenstoss (1946) previously mentioned dealing with 29 confirmed cases without associated disease of the biliary or upper part of the digestive tract created a wide

through the pyloric canal into the duodenum Five cases of the second disorder have been described by Comfort Weber Bag genstoss and Kiely (unpublished) Pathologically the lesion is identical with that of *regional enteritis* The *stomach* and duodenum may be affected when the small bowel is the major seat of involvement or they may be more conspicuously involved than the small bowel

The Liver Gallbladder and Pancreas

Unprecedented accretions to our knowledge of the diagnosis and treatment of diseases of the liver and pancreas characterize the past decade Among the impelling factors to account for this were the pandemic of acute infectious hepatitis and its con geners homologous serum and inoculation hepatitis eventually determined to be of viral origin the development refinement and broadened application of hepatic function tests aspiration *biopsy of the liver* and *improvement of the treatment regimen* for hepatic cirrhosis Moreover the exposure of countless num bers of military personnel to diseases prevalent in the tropics necessitated increasing familiarity with hepatic disorders or complications that result from amebiasis bacillary dysentery malaria schistosomiasis and leishmaniasis The nature and inci dence of cirrhotic sequelae of acute viral hepatitis have been the subject of much speculation and investigation The illuminating *contributions of Elman in acute pancreatitis* and of *Comfort* and his associates in chronic pancreatitis have made the entire pro fession more conversant with these entities which is evident from numerous recent reports dealing with acute and chronic pancreatitis and pancreatic lithiasis

Tests of hepatic function —American investigators have par ticularly distinguished themselves in this field The multiplicity of tests and the composite studies of hepatic function carried out *in large* institutions have made it difficult for the practitioner to appraise and select those least difficult technically In H R Butt s (1949) opinion tests which may aid in differentiating intrahepatic and obstructive jaundice are the *bilirubin alkaline* phosphatase urobilinogen Quick prothrombin time thymol *turbidity* test and duodenal drainage In the absence of jaun dice tests for retention of sulfobromophthalein (bromsulfalein) dye the cephalin cholesterol flocculation test and the thymol *turbidity test* are indicated

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spread renewal of interest and many subsequent reports by others confirmed their conclusions However there remains the problem of early diagnosis and treatment especially as related to the symptoms arising from insufficiency of the external secretion and the satisfactory control of pain

Tests of pancreatic function —With the elaboration and refinement of secretin the secretagogue effect of mecholyl chloride and urecholine and the development of the Agren Lagerloff double lumen tube direct examination of the duodenal contents for volume pH values concentration and total excretion of bicarbonate and enzymes has been made possible It is unfortunate that the procedure is too involved for daily practical application Opinion too is divided as to the diagnostic value It is likely that simpler dependable tests will be evolved like that of Meuther and Knight (1949)

Cytologic diagnosis of carcinoma of extrahepatic bile ducts and pancreas —B B V Lyon as early as 1923 reported finding cancer cells in the gastric secretion but this aspect of cytologic diagnosis was not pursued McNeer and Ewing (1949) diagnosed pancreatic carcinoma in two cases from presence of exfoliated cancer cells in the duodenal secretions Several months later Lemon and Byrnes (1949) reported observations on 16 cases

Intestinal Tract

Small intestine —In the past decade striking progress has been made in the knowledge of the normal and also morbid physiologic processes in the pathology diagnosis and treatment of diseases of the small intestine Lack of space does not permit detailed consideration here Use of the Miller Abbott tube or its modifications played a considerable role

Colon and rectum —The literature is replete with articles on chronic ulcerative colitis carcinoma diverticulitis polyps and protozoal infestation but there are no outstanding new developments Much interest has been manifested in lysozyme a mucolytic enzyme present in the stomach and intestines which some observers believe may initiate the lesions of regional enteritis and chronic ulcerative colitis The investigations of Almy Kern Jr and Tulin on normal subjects confirmed the important role that emotional stress plays in the alteration of colonic function similar in degree and kind to those alterations seen in patients with irritable colon

Notes on treatment—Reports are contradictory as to the efficacy of the sulfonamides during the acute stage of bacillary dysentery However most authorities agree that they reduce the carrier rate following the acute phase Streptomycin was found to be uniformly effective in relieving the symptoms of tuberculous enteritis H H Anderson and associates (1949) have found the theoarsenites highly effective and superior to all other arsenical amebacides They are the trivalent analogues of carbarsone U S P J D Hughes (1950) administered aureomycin to a series of patients with refractory amebiasis with encouraging results However the optimal dosage schedules have not yet been established

—GEORGE B EUSTERMAN

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Colon and rectum —The literature is replete with articles on chronic ulcerative colitis carcinoma diverticulitis polyps and protozoal infestation but there are no outstanding new developments Much interest has been manifested in lysozyme a mucolytic enzyme present in the stomach and intestines which some observers believe may initiate the lesions of regional enteritis and chronic ulcerative colitis The investigations of Almy Kern Jr and Tulin on normal subjects confirmed the important role that emotional stress plays in the alteration of colonic function similar in degree and kind to those alterations seen in patients with irritable colon

to be the action of gastric acids on the sensitive esophagus treatment is directed at eliminating the factor responsible for the presence of acids Therefore in cases of short esophagus and ulcer the hiatal hernia must be repaired Nonoperative treatment in this series included dietetic management dilatation of the esophageal stricture or institution of a permanent duodenal tube Such methods resulted largely in only transitory improvement In patients with esophageal and gastric ulcer removal of the gastric lesion may have a curative effect If the esophageal ulcer is caused by a possible acid production from ectopic gastric mucosa treatment must be dietary possibly with dilatation of the constricted segment Excellent results were obtained in all patients so treated

[The fact that 11 of the 27 cases (40 per cent) were in children in the first decade of life seems unusual In a series of 220 cases of esophageal hiatal hernia of the short esophagus type reported by Olsen and Harrington (J Thoracic Surg 17 189 209 April 1948) only 5 per cent were in children under 10 The prominence of vomiting and hematemesis in children has also been reported in individual instances by American observers It is much less frequent in adults especially in the absence of stricture or marked ulceration.

Although the shortened esophagus is undoubtedly of acquired origin in most adults such shortening is probably of congenital nature in children and due to circumstances brought about by delayed embryonal descent of the stomach. Thomsen s title may be misleading since the ulceration associated with short esophagus is almost invariably of the diffuse type qu te di tinct anatomically and morphologically from the familiar chronic peptic ulcer of the stomach This type of ulceration can only be identified by esophagoscopic exam nation —Ed.]

Experimental Observations on Cardiospasm in Man are reported by Stewart Wolf Thomas P Almy and Catherine R Lee[2] (Cornell Univ) Fourteen subjects who complained that swallowed food seemed to stick in the retrosternal region were studied and comparison made with 20 asymptomatic controls X rays of the patients showed obstruction to the flow of barium into the stomach

The studies indicate that the dilated elongated and obstructed esophagus of cardiospasm may be the end state of a process which in early stages is reversible and which is never entirely static The principal mechanism which participates in this process is irregular contractile activity of the lower two thirds of the esophagus which fails to propel the bolus smoothly and often leads to regurgitation A second mechanism involves localized obstruction just above the cardia

(2) G t oent ol gy 13 401 4 1 Nov mbe 1949

THE ESOPHAGUS

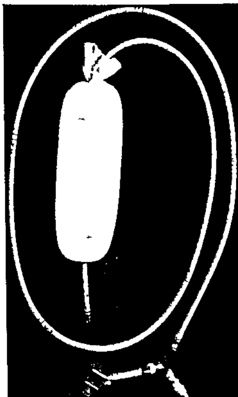
Peptic Ulcer of Esophagus can no longer be considered a rare lesion Gregers Thomsen[1] (Copenhagen) reports 27 cases seen in the University Hospital since 1936 There was no appreciable sex difference however the disease usually occurred in children under age 10 and in adults over age 30 In 18 patients the lesion coexisted with short esophagus and symptoms were vomiting hematemesis, pain and difficulty in swallowing Severity of symptoms varied in children and adults In children vomiting was an outstanding complaint usually occurring immediately after or during a meal All children also had had hematemesis of varying degrees of severity It was characteristic that some children felt best when sitting because of epigastric pain or pain on swallowing when in a horizontal position In all symptoms had been present from birth or from the first months of life Adults with short esophagus and esophageal ulcer mostly complained of retrosternal pain at times radiating into the back when food passed the esophagus In addition they had difficulty in swallowing Only a few reported regurgitation and none had had hematemesis Symptoms had lasted 6 months to 10 years Nine adults with esophageal ulcer only had similar complaints In four patients the esophageal lesion coexisted with gastric or duodenal ulceration

In 21 patients characteristic ulcer craters were demonstrated on x rays In all an esophageal constriction was present around the ulcer caused in acute cases by edema and inflammatory changes and in chronic cases by fibrous changes Short esophagus with a large hiatal hernia is easily diagnosed The small hernia is more difficult to diagnose and is best looked for with the patient on his right side in the Trendelenburg position Demonstration of irregular folds of gastric mucosa above the diaphragm is decisive Esophagoscopy may confirm diagnosis although failure of the instrument to pass the constricted area is not reliable evidence for a negative diagnosis

Since the immediate cause of peptic esophagitis is thought

(1) Act rad 1 32 193 209 1949

municates with the upper six holes of the tube and the metal tip is readjusted to communicate with the lumen containing the three lower holes By this arrangement the lumen previously used for suction now inflates the latex bag and the



Fg 94—P p d m d fi t f M ll Abbott t b f ph g l tamp d d g g (C t y f B tt C B d C b S G t oe t l gy 13 144 152 A g t 1949)

three lower holes and tip are available for feeding (Fig 94)

The authors treated three patients with bleeding esophageal varices by cardioesophageal compression A Miller Abbott tube was passed transnasally into the stomach and distended with water containing 20 cc diodrast® With this procedure the tube is gently pulled up against the cardia until

probably due to forceful contraction of the diaphragm and reduced activity in the lower half of the esophagus Both mechanisms were observed not only in patients with cardiospasm but also in healthy persons under stress In general esophageal hypermotility and dysrhythmia were more prominent in early cases and those in which esophageal obstruction was milder and more variable In the evolution of the disorder in an individual patient one mechanism may supplant the other In only one case were x rays available from the time of onset of symptoms The series of films supports the idea that hypermotility and generalized constriction precede the stage of dilatation and atonia in the esophagus

As a group patients with cardiospasm are dour humorless wary suspicious noncommittal and offensive rather than aggressive in their dealings with day to day problems They are given to suppressing rather than expressing their conflicts and feelings They are circumstantial bear grudges and brood unusually over minor slights and humiliations The attitudes and behavior may be characterized as ruminative and rumination is suggested by their esophageal dysfunction In all patients in the series it was possible to correlate episodes of symptomatic exacerbation and remission with variations in life situation feeling state and attitude In the short term experimental situation variability in degree of esophageal obstruction was demonstrated in association with changes in the emotional state

[Though definitive proof of the psychogenic origin of disease is extremely difficult here is another good example of use of the experimental approach in an attempt to elucidate the problem Winkelstein (1944 YEAR BOOK OF GENERAL MEDICINE p 615) is convinced that in most cases cardiospasm is a psychosomatic disorder One is also reminded in this connection of those interesting and refractory cases of diffuse esophageal spasm as well as the spasms of cardia or esophagus reflexly engendered by disease of the abdominal viscera and other extraneous factors —Ed]

Management of Massive Esophageal Hemorrhage with Tamponade and Thrombin is discussed by Clair B Barnett and Sidney Cohen[3] (Wadsworth Gen l Hosp Los Angeles) Direct pressure can be exerted on the bleeding point with an inflated balloon attached to a Miller Abbott tube However the original Miller Abbott tube may be adapted so as to increase surface contact with the esophageal mucosa and to permit gavage A large latex sheath is substituted which com

(3) Gastroenterology 13 144 15 August, 1949

slowly instilled through a Levin tube temporarily placed in the upper esophagus The tampon should prevent too rapid passage of thrombin past the cardia and the bleeder will be bathed in a strongly hemostatic solution During this procedure the patient should be in Fowler s position to prevent aspiration Thrombin may be used every 4-6 hours during the first 24 hours

The possibility of variceal hemorrhage is strongly suggested when other evidence of portal hypertension such as ascites splenomegaly or dilated superficial abdominal veins exist Liver failure manifested by jaundice abnormal liver function tests and hepatomegaly also supports the possibility that an upper gastrointestinal hemorrhage is secondary to ruptured varices Since cirrhotic patients may also bleed profusely it seems reasonable to discontinue tamponade if the patient continues to hemorrhage after a few hours Further tarry stools do not necessarily indicate fresh bleeding suctioned gastric contents serial blood counts and sphygmomanometer readings are better aids in deciding whether bleeding is continuing

[Any procedure which gives promise of tiding over a patient in the face of such a serious emergency is very welcome. It is not curative of course and presupposes ready access to the proper equipment as well as technical skill The authors properly call attention to the pioneer work of Rowntree and his associates (J A M A 135 630-631 Nov 8 1947) in the development of this procedure.—Ed]

THE STOMACH AND DUODENUM

Phenomenon of Peptic Ulcer H Necheles[4] (Michael Reese Hosp) analyzes some established facts and most probable theories of peptic ulcer etiology The cause of ulcer is unknown The theory that hyperacidity and hypersecretion break down the resistance of gastric mucosa causing the ulcer does not adequately explain the areas of predilection in the lesser curvature and prepyloric areas of stomach and upper duodenum and the chronicity characteristic of ulcer A devitalized area must exist before digestion can occur otherwise the entire stomach and intestine would be digested

This devitalized area is most probably caused by vasocon

(4) Am. J D g t. D 16 237 242 J ly 1949

definite resistance is encountered then secured against the upper lip with adhesive tape An x ray or fluoroscopy should reveal the upper pole of the bag at the juncture of cardia and esophagus Intermittent aspiration of the gastric contents is used to detect recurrent hemorrhage Satisfactory hemostasis



Fig 95 —F lm howing d fied M ll r Ab tt tube t mp n g l r soph gu and balloon g ut nt ca d a f st m l Balloon w s fill d w tl 20 c d d to and 100 w t r Dot outl e balloon (C rt y of B n tt C B d C he S Ga troe terol gy 13 144 152 A g t 1949)

should be established in 24 72 hours Tamponade has been maintained for as long as 72 hours without evidence of sub sequent pressure necrosis It can be quickly re established when necessary if the balloon is deflated and the tube slipped into the antrum for a further 12 24 hours A fourth patient was treated by intraesophageal pressure using the modified tube (Fig 95) Three patients received thrombin instillations A solution of 10 cc thrombin in water may be sipped or

denum where pH is 6 5 a level at which there is no peptic activity Acid secretion is within normal range in about half of duodenal ulcers and normal or low in most gastric ulcers Psychic disturbances may produce as well as aggravate an existing ulcer

It is suggested that gastric motility is the important factor in peptic ulcer Beneficial effects of vagotomy are due to gastric relaxation which abolishes pain and permits healing Necheles believes that vagotomy is never complete post vagotomy relapses are predicted when the stomach recovers tonus

Atropine and similar drugs have doubtful effect on the volume and acidity of secretion in the normal subject and in ulcer patients However they do lower gastric tone and motility and counteract acetylcholine vasoconstrictor acidity

[Necheles disarms criticism by stating at the outset in capital letters that the cause of ulcer is unknown And obviously he doe not worship at the altar of hyperacidity But the vascular theory of ulcer genesis has increasingly fewer adherents in the light of accumulating evidence There are *many straws in the wind pointing to the actual or contributing factors* f the cau e or cause but at present your guess is a good as mine —Ed]

Gastric Response of Man to Acid Test Meal Following a rise of gastric acidity some process must occur to restore the acidity to resting values That duodenal regurgitation is not essential to this process has been demonstrated by aspiration of duodenal contents It has been suggested that the stomach secretes a neutral diluting fluid responsible for the reduction of acidity or that such fluid originates in the duodenum To evaluate these concepts of acid neutralization Gordon E Bermak and J Doupe[5] (Univ of Manitoba) studied the gastric secretory response to acid solution by using constant duodenal suction and phenol red to serve as an index of gastric acid dilution The results indicate that although duodenal regurgitation decreases the emptying time of the stomach it is not essential for reduction of acidity of an acid test meal It was concluded that in response to acid instillation the stomach secretes one or more substances which reduce acidity by dilution

Measurements of pH in Gastrointestinal Tract M Pantlitschko and J Schmid[6] (Univ of Vienna) determined pH in the duodenum stomach gastrectomy stump and distal loop

(5) C d J R h S t E 27 90 9 Ap 1 1949
(6) G t t l g 75 138 146 1949 50

striction spasm and other vascular changes in the gastric arteries Obstruction of end arteries, found in the pyloric antrum on the lesser curvature and in the duodenal bulb results in ulceration this mechanism explains the higher percentage of peptic ulcer occurring in acute or subacute form postoperatively after burns in polycythemia vera and in marantic patients

To explain the devitalized ulcerated areas in the otherwise normal person the vagus acetylcholine mechanism is offered Product of vagal effect acetylcholine increases gastric secretion and motility and causes vasoconstriction of gastric blood vessels Reduction in blood flow in the areas of predilection that are regions of end arteries may then produce hypo or anoxemia of tissue in these areas Since increased and apparently continuous vagus stimulation occurs in ulcer patients it is possible that increased or continuous vasoconstriction followed by anoxemia may be present in these areas Acute ulcer follows and under continuous vagal effect may become chronic

In favor of the acid theory of peptic ulcer are the incidence of peptic ulcer following bile or pancreatic duct ligation the Mann Williamson operation histamine in beeswax ulcer the prevention of ulcers by surgery and the effect of antacids in healing or prevention of ulcer in man and experimental animals However the experimental ulcers are acute occurring only in malnourished animals and when gastrointestinal physiology is disturbed In 10 000 dog autopsies Necheles found no instance of chronic peptic ulcer in normal animals Although antacids offer patients pain relief for several hours they neutralize gastric acidity for only short periods Alkalis affect motility more than acidity does relaxing the pylorus and duodenum and enhancing gastric emptying It is possible that chronicity hemorrhage and perforation may be related to acid pepsin concentration

Against the acid theory are the following facts Ulcers are found in the esophagus lower duodenum jejunum ileum and colon without sufficient acidity to cause digestion Duodenal ulcer occurs in diabetes with low acidity Hyperchlorhydria is often found in normal subjects and hypochlorhydria in ulcer patients Vagotomy has relieved ulcer symptoms without altering the hyperchlorhydric state Most ulcers are in the duo

in the volume of gastric juice secreted but after administration of salt solution volume and acidity increase considerably and are reduced but slightly by fasting for 24-48 hours This is in striking contrast to the great reduction in gastric secretion produced by fasting in Pavlov pouch dogs or in animals with vagally denervated total pouches Blood chemical changes reduction in gastric secretion and death seem dependent on the *integrity of the vagus nerve supply to the stomach* When the vagi are cut animals survive on the salt in the food and secrete small volumes of gastric juice

In most animals ulcers developed and death occurred as a result of hemorrhage or perforation In general the ulcers occurred more rapidly in animals that secreted large volumes of gastric juice This evidence confirms the view that pure gastric juice has the capacity to digest the wall of the stomach Preservation of vagal innervation has been essential for development of ulcers in either the whole stomach or the Pavlov pouch

Hypercalcemia without Hypercalcuria or Hypophosphatemia, Calcinosis and Renal Insufficiency Syndrome Following Prolonged Intake of Milk and Alkali. Charles H Burnett Robert R Commons Fuller Albright and John E Howard[9] studied six patients who had had prolonged and excessive intake of milk and alkali for peptic ulcer They presented hypercalcemia without hypercalcuria or hypophosphatemia normal serum alkaline phosphatase value renal insufficiency with azotemia mild alkalosis calcinosis (manifested especially by an ocular lesion resembling band keratitis) and improved on intake low in milk and alkali

Biochemical abnormalities were at first inspection those of advanced renal insufficiency but definite differences from the pattern usually seen in uremia were detected Instead of acidosis five patients had moderate alkalosis Alkalosis could not always be attributed to alkali ingestion and vomiting Serum protein levels were not as low as might have been expected and three patients had hyperproteinemia from increased serum albumin concentration

Though it was impossible to state in most instances that *hyperparathyroidism did not exist many circumstances sug*gested that it did not These included lack of hypophospha

(9) N w E gl nd J Med 240 787 794 M y 19 1949

with the aid of an antimony electrode The antimony electrode was fitted into the bulb of an Einhorn duodenal tube and from it a wool thread steeped in saturated potassium chloride solution formed an electrolyte bridge to the calomel electrode

Neutral pH values show a shift in distal direction in gas tritis and gastric and duodenal ulcers Acidity in the bulb of the latter is below pH 5 Localized gastritis (antrum gastritis) shows higher acidity in the involved area of the mucous mem brane than in nearby areas This causes a depression in the pH curve Food poisoning often leads to a lowering of pH a short distance beyond the papilla of Vater in addition to signs of diffuse gastritis The pH after operations on the stomach is constantly lower than normal in the distal loop This is particularly striking in cases of peptic jejunal ulcer

Secretory Studies on Isolated Stomach of dogs were car ried out by Lester R Dragstedt Edward R Woodward Wil liam B Neal Jr Paul V Harper Jr and Edward H Storer[7] (Univ of Chicago) The stomach was isolated with preserva tion of the blood and vagus nerve supply and quantitative collections of gastric secretion were made from 81 to 282 days When the entire stomach was isolated and the lower end of the esophagus united to the open end of the duodenum av erage maximal secretion for each 24 hours was 973 cc After similar isolation with the lower end of the esophagus sutured to the side of the jejunum, average maximal secretion in each 24 hours was 906 cc When the antrum was not included with the isolated stomach but was left attached to the duodenum and sutured to the open end of the esophagus average maxi mal secretion was 1 687 cc These data support the concept that the antrum of the stomach plays a special role in gastric secretion

Continued loss of such large amounts of gastric juice re sulted in progressive hypochloremia alkalosis dehydration azotemia and death in 4 12 days when the only salt supplied was that present in the stock diet These changes can be pre- vented and life preserved for long periods by the intravenous injection of 1 2 L isotonic NaCl solution daily If salt replace ment is discontinued even after several months prompt de mineralization dehydration and death follow The blood chemical changes are accompanied by a pronounced reduction

(7) Arch. S rg 60 1 20 January 1950

is overlaid with an alcoholic benzidine solution (6 Gm benzidine base in 100 cc ethyl alcohol) drop by drop to obtain a contact ring A greenish ring at the area of contact indicates a positive reaction The ring spreads into the benzidine solution immediately or in up to two minutes Intensity or gradient of color depends on the blood concentration When testing for blood in vomitus and gastric contents water is added to either in half the volume of material used the mixture is filtered and the test carried out as before For urine *when only a few red blood cells are found microscopically* (4 8 red blood cells/high power field) the pecimen is centrifuged the bottom 0 1 cc containing sediment is transferred to a clean test tube 0 4 cc distilled water is added and the test is continued as before

In various ulcerative and nonulcerative gastrointestinal conditions about 32 per cent of specimens gave positive reactions to this benzidine test 68 per cent gave positive reactions with the ordinary method Gastrointestinal carcinoma specimens however gave 99 + per cent positive reactions with both methods The authors technic eliminates most substances producing false positive reactions as follows (1) filtration *of the stool suspension eliminates* blood containing particles of meats (thus meat free days are unnecessary preceding the test) oxidase containing particles of foods particles of animal charcoal and insoluble metal salts (iron copper etc) (2) the acetic acid destroys soluble oxidases Also with the contact layer or ring test soluble hemoglobin compounds give true positive blood reactions in dilutions up to 1 100 000

[From time to time there have been modifications of the standard benzidine and guaiac tests but reports on their clinical effectiveness in all forms of benign and malignant gastrointestinal ulcerative processes have been infrequent Such evaluation has recently been made by Hoerr Bliss and Kaufman (J A M A 141 1213 1217 Dec 24 1949) They found the benzidine and orthotoluidine tests too sensitive to be useful for routine testing of tools from patients who had not been prepared with a meat free diet. The guaiac te t however proved at sfactory e pe c ally when performed on feces sm ared directly on filter paper or on feces f om a rectal glove One d scussant of their paper favored the Alvarez and Wright modification of the Gregerson benzidine test The spectroscopic examinat on is very dependable Because we are daily becom ng more cancer consci us a d becau e carcinoma of the gastrointestin l tract is often accompanied by occult blood in the feces more frequent resort to such tests should be made In fact some well known hospitals perform them routinely when an ulcerating lesion or bleeding is under su picion and in one inst tut on it i reputedly done on all patients with any suggest on of abdominal d sea e —Ed]

Melena Study of Underlying Causes based on 293 cases of gastrointestinal bleeding in which melena was a prominent

temia accompanying the hypercalcemia lack of hypercalcuria lowering of serum calcium on low calcium intake and absence of skeletal demineralization and increased serum concentration of alkaline phosphatase Other conditions in which renal failure is often associated with hypercalcemia were excluded Such conditions are acute osteoporosis hypervitaminosis D sarcoidosis myelomatosis and generalized carcinomatosis In chronic Bright s disease with uremia acidosis with hypocalcemia and hyperphosphatemia is the usual picture

It has previously been suggested that milk and alkali adversely affect kidney function by producing alkalosis Among the authors patients no episodes of acute alkalosis with accompanying severe dehydration hypochloremia and azotemia were known to have occurred The question of whether the patients had pre existing renal disease could not be settled Prolonged hypercalcemia and renal failure such as existed in the patients studied has not previously been recorded Absence of hypercalcuria and lowering of serum calcium levels following low calcium intake suggest interference with renal secretion of calcium the mechanism of which is unknown

The pathogenesis of the condition described in the authors opinion is as follows excessive intake of milk (containing large amounts of calcium and phosphorus) and alkali kidney damage tendency to fixation in urinary calcium secretion hypercalcemia tendency to supersaturation with calcium phosphate and calcinosis

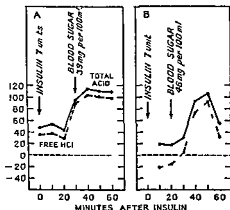
Simple Benzidine Test for Occult Blood in Feces Workers using ordinary laboratory procedures encounter many factors other than occult blood which produce positive reactions in stools of patients with suspected gastrointestinal bleeding For more accurate results M B Levin and J Y C Watt[1] (Baltimore) devised a technic which eliminates known false positive reactions

METHOD—A small portion of feces is emulsified in distilled water then passed through filter paper (Whatman no 5 or more retentive paper) into a clean test tube to obtain a clear filtrate If the filtrate is clouded due to a breach in the paper it is refiltered To 3 cc filtrate 8 drops of 50 per cent aqueous acetic acid or glacial acetic acid is added To the resulting mixture 8 drops of hydrogen peroxide (C P 3 per cent) is added and shaken The final mixture

(1) R G t oe te l 16 650 651 A g t 1949

stained with blood pigments or altered blood The occurrence of such stools usually implies that bleeding has its source in the upper digestive tract. Therefore one wonders if the term applies to bloody discharges which have their origin in lesions of the colon and rectosigmoid with rare exceptions I doubt it A slowly oozing lesion in the cecum plus lowered bowel peristalsis may give rise to melena but distal to this the stool usually is characterized as bloody or sanguinous That next to peptic ulcer bacillary dysentery was the most frequent cause of melena is an interesting observation —Ed]

Insulin Test for Vagal Section B N Brooke[3] (Univ of Birmingham) states that when an acid secretion is obtained with an insulin test vagus nerve fibers are intact Before the



Fg 96—R p t ln 01 u t /kg b dy w ght *A* p pe t p e. *B* d fi t p t p 10 d y ft p t n V t l l p se t m ll l t f N/10 HCl N Cl q l t t 100 ml g t j e (C te y f B ook B N L t 2 1167 1170 Dec 24 1949)

test can be regarded as satisfactory blood sugar level must be brought to 45 mg /100 ml or below

If an acid response similar to that obtained before vagal section occurs during the early postoperative period a complete nerve trunk probably has been overlooked (Fig 96) There are patients however who show no response to an adequate stimulus during the first month postoperatively but secrete acid when tested six months later In this group the acid response does not show the steep rise and high final level characteristic of the preoperative pattern (Fig 97) To avoid unreliable results the tests should be done at least six months after operation After a 12 hour fast the patient is given 10

(3) Lanc t 2 1167 1170 D c. 24 1949

clinical sign is presented by Harold Lincoln Thompson and DeVere W McGuffin (Los Angeles) The sources of hemorrhage included all portions of the gastrointestinal tract except the anus

There were 87 cases of peptic ulcer 29 6 per cent of the entire series Hematemesis was present in 79 5 per cent Fifty five per cent of cases occurred in the fourth through the sixth decade a factor of importance when correlated with mortality Most patients were treated medically with a mortality of 24 9 per cent

There were 27 cases (9 per cent) in which esophageal varices were complicated by melena The highest death rate in the nonmalignant conditions—70 5 per cent—occurred in this group This fact indicates the urgent nature of gastrointestinal bleeding from this source

There were 23 cases of carcinoma of the stomach The mortality was 90 per cent in the 10 nonsurgically treated cases 33 per cent in 3 in which the lesion was resectable and 60 per cent in 10 in which it was nonresectable

Of the miscellaneous sources of hemorrhage from the stomach hiatus hernia heads the list with five cases Exclusive of peptic ulcer there were only six cases of melena arising from the small intestine

Bacillary dysentery was the second most common cause of melena in this series Also of conditions localized in the large intestine it comprised the largest number 63 Significantly 73 per cent of these cases occurred within the first decade Mortality was low

There were 18 cases of carcinoma of the rectosigmoid Mortality was 62 5 per cent in 8 cases in which surgical treatment was employed and 90 per cent in 10 treated nonsurgically Other sources of bleeding from large intestine included idiopathic ulcerative colitis (16 cases) Medical treatment was given in 14 with a mortality of 35 6 per cent Surgical treatment in two cases was successful There were 11 cases of diverticulitis of the colon of which 63 6 per cent occurred in the descending colon and sigmoid Most of the patients with diverticulitis were females Nonsurgical treatment was carried out in all without mortality

[By melena is meant the passage of dark pitchy and grumous stools

(2) J A M A 141 1208-1213 Dec. 24 1949

Mechanism of Postgastrectomy Dumping Syndrome The stomach functioning as a reservoir normally evacuates a mixed meal in three or four hours at a rate of 10 15 cc/minute In patients deprived of a normal gastric reservoir by gastroenterostomy or subtotal gastric resection ingested food may enter the jejunum almost immediately and give rise to symptoms such as sweating tightness or pain in the epigastrium nausea weakness palpitation feeling of warmth vertigo and even collapse These symptoms the dumping syndrome may occur after all meals or only after certain meals and vary in severity Some patients find that avoidance of certain foods or of liquid may prevent symptoms

Production of symptoms has been ascribed to (1) hypoglycemia secondary to the hyperglycemia resulting from rapid absorption of carbohydrate from the jejunum (2) the hyperglycemia of the postprandial hyperglycemic phase of absorption and (3) mechanical distention of the jejunum Both early postprandial symptoms due to mechanical distention of the jejunum and late postprandial symptoms due to hypoglycemia are said to occur

To determine the mechanism of production of symptoms Thomas E Machella[5] (Univ of Pennsylvania) performed experiments on 16 patients manifesting the dumping syndrome and on control subjects with intact stomachs Diet included normal mixed meals and test meals of cooked cereal cream milk sugar toast butter and egg calculated to contain 75 Gm carbohydrate 25 Gm protein and 38 Gm fat Tests were made with hypertonic solutions of protein hydrolysate and dextri maltose[*] with glucose or sucrose given orally and intravenously and with sodium sulfate instilled in the jejunum An air inflated balloon was used to distend the intestine in some experiments Effectiveness of atropine and of fluid and sugar free meals in preventing symptoms was also studied

Symptoms occurred toward the end of or shortly after a mixed meal when hypertonic food passed into the jejunum Although hyperglycemia was associated with blood pressure rise and increased pulse rate during this period hyperglycemia did not cause the symptoms Hypoglycemia was not found in any patient during symptoms Dumping occurred after intrajejunal instillation of glucose before hyperglycemia de

(5) A S g 130 145 159 A g 194

units of insulin intravenously With this dosage the blood sugar will be depressed adequately in 82 per cent of cases Blood sugar levels are measured 30 and 40 minutes after insulin injection

For routine purposes only a postoperative test is necessary When the vagi are intact the quality and quantity of

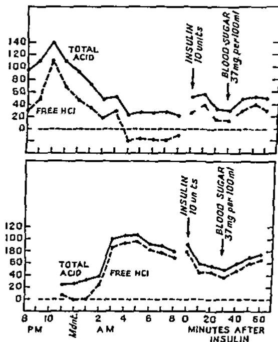


Fig 97—Re lts f ns l n te t a t o es x m th ft g l t n w t t g str nt r tomy how g d et n d ng n ght b f e t t Immed ate p t p at te t w neg t e Test t x m ths b w d ly l ght acd p n e V t l s te p es ts m ll lit f N/10 HCl N Cl q l nt to 100 ml g st y (Court y of B k B N L t 1167 11 0 De 24 1949)

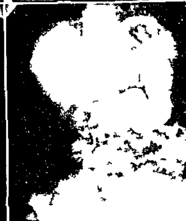
acid response to hypoglycemia bear no more relation to the ordinary acid level in the stomach than does the response to histamine Lack of acid secretion after vagotomy when the blood sugar is reduced to 45 mg or less does not make it certain that all nerve fibers have been cut

[It is to be hoped that the modification of the test and the other recommendations proposed by the author will eliminate in whole or large part the discrepancies frequently now encountered —Ed]









F g 98 (top l ft) —P p t e t m b how ng f ly g d t d p tal

F g 99 (t p ght) —S m ı t t k ft g my N t mpl t y th t m d l t t N ı t lt w

F g 100 (b ttom l ft) —S m p t t m d ; F fty p t hou t

F g 101 (b ttom ght) —S p t t m h ft g t my Good y f t d f ı t I

(C t y of I F t l Am J R tg 1 63 66 5 J y 1950)

veloped and during oral ingestion of glucose or sucrose but did not occur when glucose was injected intravenously

The dumping syndrome was also reproduced in control subjects by intrajejunal instillation of hypertonic solutions of glucose protein hydrolysate and sodium sulfate and by distention of the jejunum with an air inflated balloon To produce symptoms meals must possess ingredients of high osmotic pressure usually sugars and sufficient fluid to dissolve them and still yield a hypertonic solution Vomiting offered complete relief from symptoms by removing the cause of distention When hyperperistalsis resulted in rapid stool evacuation symptoms did not occur Omission of fluids from meals and administration of atropine in physiologic doses before meals prevented symptoms though the exact mechanism of preventive action of atropine is not clear Vagotomy does not prevent symptoms

It is suggested that the early postprandial dumping syndrome is due to distention of the jejunum by outpouring of fluid by the jejunal wall in an attempt to dilute the hypertonic food solution passed along by the nonretentive stomach rather than to mechanical distention by ingested food bulk

[The gist of this investigation was recorded in discussion of an article by Schechter and Necheles on the subject (1949 YEAR BOOK OF MEDICINE p 706) —Ed]

Roentgen Studies of Upper Gastrointestinal Tract in Vagotomy were made in 80 male and 3 female patients aged 20 72 by Frank Isaac Richard E Ottoman and Joseph A Weinberg[4] (Birmingham Veterans Admin Hosp Van Nuys Calif) Postvagotomy check ups were possible in 75 at one week 72 at one month and 50 at six months

The most striking but the least constant change was loss of gastric tone with dilatation (Figs 98-101) Initially in the postvagotomy period 57 4 per cent showed this change after six months it was present in 33 4 per cent Delayed motility was present in 80 per cent in the early postoperative period six months later 41 per cent still had six hour retention The most constant postvagotomy change was decreased peristaltic action which was found in 87 per cent in the early postoperative period and in 48 per cent at six months After six months more patients showed complete return to normal following

(4) Am J Roentgenol 63 66 75 Jan ry 1950

simple vagotomy combined with gastroenterotomy than following simple vagotomy alone Whether the operation was performed by the thoracic or abdominal route seemed of little importance Most patients with a demonstrable ulcer crater in the duodenal bulb preoperatively showed disappearance of the niche after vagotomy

Definite alterations were noted in the pattern and motility of the small intestine as a result of vagus section (Figs 102 105) The most significant pattern changes consisted of moderate dilatation of the second and sometimes the third portion of the duodenum These changes tended to disappear after six months Delayed motility in passage of barium meal was noted consistently and showed little tendency toward improvement over six months Less constant small intestine alterations included pooling of the meal segmentation of opaque filled loops and flocculation of barium

Neurodigestive Asthenia Gastroenterologic Analogy to Neurocirculatory Asthenia Z Maratka[6] (Charles Univ Prague) describes neurodigestive asthenia as a condition of poor health with gastrointestinal symptoms and delicacy sen

TABLE 1—SYMPTOMS AND SIGNS OF AUTONOMIC LABILITY

	%
Weakness	78
Headache	75
Sweating	46
Dysmenorrhea	32
Mydriasis	50
Dermographism	25
Exophthalmus	4
Basal metabolic rate over + 20%	17
Abnormal vegetative reflexes	57
Solar syndrome	91

N m l g t t fl oc loca d l fl x b dyca di p t —15/m th t t fl tachycard up t + 20/m n l t t fl b dy d up to —8/m S l y d m — p n on p lp t f p n ly p lsat g a rta p g t m.

sitiveness and lowered efficiency of the digestive tract but no organic lesion It affects young persons with predominantly asthenic body build symptoms and signs of autonomic lability and more or less distinct psychoneurosis

In 50 patients the most common complaints were epigastric discomfort a sense of fulness after meals belching nausea indigestion after eating large meals irregular bowel

(6) G t oe t logi 75 228 237 1949 50

The patient is most often an unmarried woman aged 18 25 who is emaciated and has a repugnance to food usually associated with amenorrhea and constipation Examination reveals severe cachexia dry hypertrichotic and occasionally scaling skin and cold extremities Bradycardia hypothermia and hypotension are found Cheilitis glossitis gingivitis and dental decay are common Laboratory studies are normal except for low basal metabolic rates of — 20 40 per cent flat glucose tolerance curves and abnormal electroencephalograms The patient is indefatigable and active out of proportion to her malnutrition

Simmond s disease presenting a similar clinical picture can be readily differentiated It occurs in middle aged women and is precipitated by physical illness Weight loss is at first minimal later profound and dramatic There are premature aging wrinkled skin loss of pubic and axillary hair loss of sexual desire and atrophy of sex organs lassitude and weakness low basal metabolic rate and a disturbed glucose tolerance curve Amenorrhea is present in only one half of the cases

In psychologic development the child who later develops anorexia nervosa is a good fanciful little girl with vivid imagination She is lonely and seclusive fits poorly into the family pattern and does not make friends easily She is usually the product of unstable parents with a food fetish and eating habits are under close observation She is chubby intelligent energetic and obedient in preadolescence With onset of the menarche she becomes irritable and aloof and has conflicts with her parents particularly the mother but remains dependent on the family When teased about her weight she responds with severe dieting despite a healthy appetite Anorexia comes later She becomes busy ambitious extremely conscientious and feels pushed to perfection in decorum and scholarship She obviously feels insecure

Tense hyperactive alert and rigid she walks talks and thinks rigidly She becomes a puritanical old maid introverted serious and obstinate beyond reason If married there is unsatisfactory sexual adjustment with repugnance for coitus She is moody and feels she is unwanted and a failure

The patient defends herself against the menace of society and family by rejecting food Persistent imperative recur

movements constipation diarrhea and other dyspeptic symptoms Almost all patients had cardiovascular symptoms Signs of autonomic imbalance (Table 1) were frequent

The first manifestations of this condition may be traced to childhood Puberty is critical for the onset of overt symptoms After 40 the symptoms tend to decrease or disappear One of the main characteristics is the variability of symptoms over the years

Differential diagnosis should include organic diseases of individual digestive organs and psychoneurosis with gastro

TABLE 2—DATA IN DIFFERENTIAL DIAGNOSIS OF NEURODIGESTIVE ASTHENIA AND PSYCHONEUROSIS

	NEURODIGESTIVE ASTHENIA	PSYCHONEUROSIS
Constitution	Asthenic	Variable
Onset	Near puberty	Any time
Symptomatology	Less variable	More variable
Duration of symptoms	Chronic	Intermittent or chronic
Dependability on diet	Important	Not important
Digestion previously	Poor	Good
Cardiovascular symptoms	Almost always	Often
Emotional influence	Considerable	Definite
Effect of psychotherapy	Improvement	Sometimes cure

intestinal symptoms Table 2 presents data which may aid in differentiation of the latter from neurodigestive asthenia

Etiologic factors important in genesis of neurodigestive asthenia are heredity and psychogenesis Prognosis for life is good but prognosis for cure is poor Therapeutic measures include a hygienic way of living and reassurance

[Various writers have called attention to this group of patients although they did not make the clearcut distinctions between them and the neuro with nonorganic digestive disturbances—who may be fat lean or hypersthenic Most authorities will agree that the author s conception is a distinction with a difference —Ed.]

Compulsion Neurosis with Cachexia (Anorexia Nervosa) This peculiar form of disease fully described in the last century as anorexia nervosa vividly illustrates the interrelationship between emotions and body functions it is believed to be primarily a psychologic and secondarily a physiologic disturbance Franklin S DuBois[7] (New Canaan Conn) describes the nature of the personality or psychologic disorder and the psychiatric category in which this disease is placed as fundamentally a compulsion neurosis with the major symptom cachexia

(7) Am. J Psy h t 106 107 115 A gu t 1949

little known Clinical phenomena of the disorder are similar to those of ulcer Roentgen examination is decisive in diag nosis *since it demonstrates the typical forms of the prolapse* which can be classified into three groups

In group 1 a small mucosal fold has prolapsed into the pyloric canal This form is relatively frequent On roentgen examination the outgoing peristaltic wave makes this fold apparently disappear In group 2 the longitudinally placed mucosal fold in the pyloric canal extends its free end into the duodenal bulb in the form of a mushroom like filling de fect when slight compression is exerted on the bulb filled with contrast substance This is a unilateral partial prolapse the frontal view of which is the picture just described while the profile view shows a unilateral dent in base of the bulb so that the length of the pyloric ring on this side seems to have increased Group 3 includes total or circular prolapse in which the parapyloric impression of the base of the bulb is strongly accentuated so that the pyloric canal appears lengthened and a thickening of the pyloric muscle ring is simulated as in pyloric hypertrophy The distance between the gastric outlet and the base of the bulb is considerable

When the clinical disturbances are slight treatment may first be conservative (diet bed rest drugs) Indications for operation are pronounced bleeding tendency symptoms of stenosis and attacks of pain which resist treatment Mucosal prolapse should be accepted on the strength of positive clini cal and roentgen signs even in cases in which palpation and inspection of the specimen during and after operation do not reveal any gross changes and in which macroscopically there is only gastritis Absence of gross anatomic changes raises the suspicion of prolapse and many negative operative results with positive roentgen findings represent unrecognized mu cosal prolapses Verification of atypical mobility of the mu cosa on the muscularis should never be overlooked

Prolapse of Gastric Mucosa and Its Possible Relationship with Peptic Ulcer and Upper Gastrointestinal Hemorrhage S P Bralow G H Becker S Scheinberg and H Necheles[9] (Michael Reese Hosp) report three cases in which prolapse of gastric mucosa was associated with duodenal ulcer and two in which severe upper gastrointestinal hemorrhage was asso

(9) Am. J D g t. D s. 17 65 69 M h, 1950

rent thoughts of food fit the pattern of obsession just as re peated unreasonable imperative rejection of food conforms to the pattern of compulsive action These components com bined with obvious tension formulate the obsessive compul sive ruminative tension state ending in cachexia

Constitutional predisposition is only one factor in this dis order Inanition prevents maturation and the assumption of adult responsibilities and causes suppression and rejection of sexual desire and menses It is also suggested that rejection of food is a device to atone for guilt of ambivalent reactions to parents Food rejection and inanition are rewarded by so licitude and indulgence enabling the patient to regress to in fantile reactions Some behavior changes including deviations in thought result from ill nourished organs

Many mild cases probably recover spontaneously as time brings maturity and the severance of parental ties When the disorder is fully developed the possibility of satisfactory treatment is remote and permanent recovery is improbable. Although 5 of 10 patients treated by DuBois made limited ad justments all remained introspective and stubborn and 4 con tinued to have difficulty in relations with the opposite sex

Recommended treatment consists of psycho and somato therapy Hospital or sanatorium care is essential with bed rest and semiambulation prescribed initially Six modest feed ings totaling 1 500 calories/day are supplemented with vita mins intramuscular injections of liver extract and high fluid intake Mild cathartics are given Repeated reassurance is nec essary to explain the initial uncomfortable symptoms such as gastric distention and cramps In two or three weeks food intake is increased to 3 000 3 500 calories/day Insulin in tonic doses of 5 25 units before meals enhances ability to accept the added food Exercise and occupational therapy are intro duced Little reference is made to food and diet reassurance and explanations are stressed and mental hygiene re educa tion attempted Active therapy lasts three months with a fol low up of three years desirable

Clinical and Roentgen Study of Prolapse of Gastric Mucosa into Pylorus and Duodenal Bulb According to E A Zim mer[8] (Fribourg) the fact that this type of prolapse is rela tively common and hence of practical significance is still too

(8) Schwe med Wch s hr 80 351 358 Apr 8 1950

ciated with x ray evidence of prolapsed gastric mucosa Case 1 is given here

Man 39 had a typical history of ulcer dating back 12 years For six months before admission the gnawing burning pain experienced by the patient was almost constant and was intractable to rigid medication An x ray revealed a moderate degree of prolapse of the gastric mucosa with spasm of the second portion of the duodenum (Fig 106) Operation disclosed prolapse of the prepyloric mucosa and a posterior penetrating ulcer in the second portion of the duodenum involving the head of the pancreas Figure 107 reveals the relation of ulcer to prolapse

On the basis of these and other cases the authors propose the following etiologic sequence of events leading to prolapse of gastric mucosa into the duodenum peptic ulcer gastritis hypertrophied rugal folds and eventual prolapse The original ulcer may heal but once prolapse has occurred it may recur The most frequent symptoms are vague epigastric distress with intermittent cramping bloating and a sense of fulness after meals Nausea and vomiting occasionally occur These manifestations are compatible with a variable degree of pyloric obstruction In many cases prolapse will respond to conservative management and operation is indicated only in cases of severe intractable pain persistent pyloric obstruction or repeated massive hemorrhage

[Although some roentgenolog sts are doubt g Thom ses concern ng this condition the numerous current contributions on the ubject at home nd abroad are reminders of the old saw where there is smoke there is fire —Ed.]

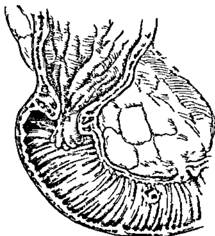
Chronic Gastritis J hn W Findley Jr Joseph B Kirsner Walter Lincoln Palmer and Theodore N Pullman[1] (Univ of Chicago) made a comparative analysis to determine the symptomatology and the gastric secretory response to histamine in chronic gastritis Three groups of patients 50 of whom showed atrophy of the gastric mucosa 50 superficial gastritis and 50 hypertrophic gastritis and a control group of 100 persons with apparently normal gastric mucosa were studied So far as possible other organic disease was ruled out

The predominant complaint of the patients abdominal pain was located most often in the epigastrium and showed little variation in incidence or time of occurrence Other symptoms likewise did not differ significantly among the groups

(1) Am J M d 7 198 06 A gu t 1949

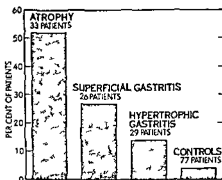


F g 106—F lm h w g prol p e f ga tr c mu osa and pa m of d ode m (Courtesy of B alow S P *t l* Am J D gest D s 17 65 69 Ma h 1950)



F g 107—S g l pec m show g lat f d od l ul t g l p ed g t c m c sa (Co t y f B l w S P *t al* Am J D ge t. D s 1 65 69 Mar h 1950)

acid (histamine) is lowest in patients with mucosal atrophy (3) Some individuals with superficial gastritis are capable of producing large amounts of acid but the mean histamine secretion is less than it is in persons with hypertrophic gastritis or in controls The incidence of anacidity in superficial gastritis is second only to that in atrophy (4) The incidence of histamine anacidity seems greater in patients with hypertrophic gastritis than in persons with normal mucosa but



F g 109—I d ce f h t mi e c d ty (Courtesy of F dl y J W J et al Am. J M d. 7 198 206 A g t, 1949)

the mean acid secretion is approximately the same This may be due to the fact that a certain proportion of individuals with hypertrophic gastritis secrete excessive amounts of acid

New Diagnostic Criterion for Gastric Syphilis is presented by Herbert Berger[2] (Staten Island N Y) who reports two illustrative cases Gastric syphilis can be diagnosed only when the patient has untreated tertiary syphilis demonstrable x ray defect and gastric symptoms The symptoms and x ray appearance must not improve under conventional therapy but should respond strikingly to specific antisyphilitic therapy In the past antisyphilitic therapy has been carried out with arsenicals and bismuth but in the cases reported response occurred after treatment by the rapid method with penicillin The advantage of the rapid method is that results of treatment are obtainable within one or two weeks Since this interval is not greater than that usually required for preparation

(2) Gast oe t l gy 14 147 151 J ry 1950

Distress when present and distinct from pain showed no characteristic pattern

The gastric secretory response to histamine was determined quantitatively in 165 patients by measuring total milligrams of free HCl total volume and the average units of free acid secreted during the hour following subcutaneous injection of histamine

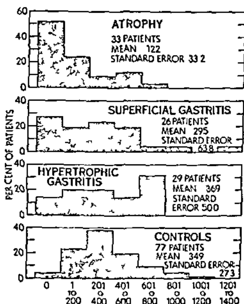


Fig 108 — Distribution of total milligrams of free HCl secreted during one hour after injection of histamine (Courtesy of Findley J W Jr et al Am J Med 7 198 206 August 1949)

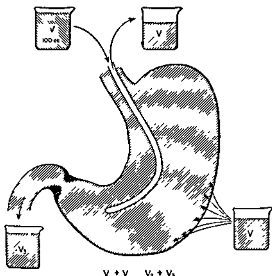
tion of histamine Patients with mucosal atrophy secreted the smallest amounts of acid and those with superficial gastritis the next smallest although two of the latter group secreted large amounts of acid The distribution is given in Figure 108

The incidence of histamine anacidity is presented in Figure 109 Significant statistical differences were found between the atrophy and control groups and between the superficial gastritis and control groups

The conclusions drawn from the study were (1) The common types of chronic gastritis apparently produce no symptoms (2) Histamine anacidity occurs most frequently with atrophy of the gastric mucosa The mean secretion of

and 23 vagotomy patients 7 days to 45 months after operation

Chloride minute output was for normal persons 0 24 m Eq./minute for ulcer patients 0 41 m Eq /minute and for vagotomized patients 0 18 m Eq /minute The chloride minute output illustrates wide fluctuations in gastric secretory activity Secretion is lost through the pylorus at the rate of 6 0



F g 110—D g m f t m h w th L n t b pl ll t t g th f tt s f l m me d d cal l t d by th dy d l t t b V_1 (l j t d — 100 t c al t g 7 mg /L ph l d) d V^1 (l m p t d 10 mi te aft j t on) m d d tly wh l V_3 (pyl ffl) d V_4 (g t t) lcul ted d cat d t t (Cou t y f B k J R *t al* S g Gy & Ob t 90 155 170 F b y 1950)

cc /minute in normal persons and ulcer patients but following vagotomy the rate drops to 3 5 cc /minute Regurgitation of duodenal contents into the stomach is more common in vagotomized ulcer patients than in normal persons or ulcer patients There was no change in the reduction of chloride minute output following vagotomy when tests were conducted over an extended period

Introduction of 100 cc perfusate containing either 500 or 750 mg acetylcholine into the stomach produced a consistent statistically significant secretory rate in normal persons ulcer

of patients with gastric conditions for operation, no time is wasted if the gastric lesion is not due to syphilis

[Occasionally there may be symptomatic improvement during or following antisyphilitic treatment of patients with nonsyphilitic gastroduodenal lesions but objective (anatomic) changes are nil Penicillin therapy represents a distinct advance In my experience fewer patients are now seen harboring late specific abdominal visceral lesions The same appears true of cardiovascular lesions Clawson (Minnesota Med 33 437 440 May 1950) called attention to this decline In the five years 1914-18 the incidence of death due to syphilitic heart disease was 17 4/1 000 autopsies It was 2 3/1 000 during the four years 1944 47 One can only speculate as to the cause of this great decline but it is reasonable to presume that improved medical education earlier diagnosis and improved methods of treatment play a considerable role —Ed]

Chloride Output Rate of Human Stomach in Healthy Subjects and Ulcer Patients, Effects of Vagotomy and Acetylcholine Studies by Dye Dilution Technic are reported by John R Brooks John M Erskine Thomas Gephart Oliva Swaim and Francis D Moore[3] (Harvard Univ) Most studies of gastric secretion have been confined to titration of free and total acidity neglecting the pepsin mucin total base and potassium content Since the acid in gastric secretion is partly neutralized by base secreted in the antrum or by reflux of the alkaline duodenal fluid titratable acidity is but a secondary reflection of total acid secretion These errors are compounded when titratable acidity is multiplied by volume units to yield milliequivalents of hydrochloric acid

Gastric secretion was investigated by the dye dilution method which depends on the introduction of a measured quantity of dye into the stomach and its aspiration 10 minutes later with the gastric juice accumulated during that period From the dilution and total quantity of dye recovered total secretion of the stomach may be calculated as well as that portion of the gastric juice lost through the pylorus (Fig 110) Analysis of aspirated gastric juice for total chloride content permits expression of gastric secretory rate predominantly traceable to parietal cell activity Results are in terms of total chloride secretion of the whole glandular cell mass/unit of time the chloride minute output Data on total gastric secretory activity in the human patient which are otherwise not available can be obtained in a few hours Studies were made on 37 normal adults 29 patients with duodenal ulcer 20 of whom were intractable to medical therapy

(3) Surg Gynec & Obst 90 155 1 0 F b u y 1950

The evidence suggests that gastric and duodenal ulcers are diseases of different pathogenesis The concept that duodenal ulcer is caused by the action of abnormal degrees of acidity over abnormally long periods is supported by the evidence Observations indicate however that gastric ulcers are not attributable to this cause

[These difference in the gastric secretory milieu of patients with duodenal ulcer and gastric ulcer largely confirm findings of previous investigators For example Dragstedt Camp and Fritz (Ann Surg 130 843 856 October 1949) pointed out that in patients with gastric ulcer acid secretion is the same or less than in normal people. The increased nocturnal secretion in patients with duodenal ulcer which may be three to four times the amount in normal persons is attributed to the neurogenic factor *hence the significance of excess acid pepsin in pathogenesis* With respect to etiology th y believe that gastric ulcer is due to a decrease in resistance on the part of the gastric wall and not to any corrosive properties of the gastric content —Ed.]

Nocturnal Gastric Secretion in Patients with Benign Gastric Ulcer Erwin Levin Joseph B Kirsner and Walter Lincoln Palmer[5] *(Univ of Chicago) compare the periodicity and* variability of nocturnal gastric secretion in patients with benign gastric ulcer normal subjects and patients with duodenal ulcer There appeared to be no significant difference in total volume in patients with gastric ulcer and normal individuals *but that in patients with duodenal ulcer was significantly* greater than in gastric ulcer patients In all three groups night secretion of gastric juice was continuous with a tendency for the average hourly volume to decrease gradually during the night Although individual variations existed in all groups *the secretory rate remained at a consistently higher level in* the duodenal ulcer patient

The total amount of acid and concentration of free hydrochloric acid secreted during the night was lowest in gastric ulcer patients Secretion of hydrochloric acid was continuous only in duodenal ulcer patients Although there were individual fluctuations in amount and concentration of free acid usually there was a constancy on successive nights in the same individual Average hourly concentration was highest in patients with duodenal ulcers and lowest in gastric ulcer patients and both groups showed a gradual decrease during the night There appeared to be no correlation between the degree of gastritis determined gastroscopically and the amount of acid produced

(5) A I t M d 30 1020 1032 M y 1949

and vagotomized patients Although the secretory rate increased in response to the drug degree of response among the three groups was not significantly different Only normal patients showed a significant increase in chloride concentration due to acetylcholine despite the change in rate of chloride minute output in all *No group revealed a significant change* in pH Similar secretory responses were produced by histamine and insulin hypoglycemia Local application of acetylcholine reduced the evacuation rate in all groups and increased the frequency of duodenal regurgitation in vagotomized patients The local effect of acetylcholine is due to its particular organic configuration and is not a nonspecific effect of its chemical constituents

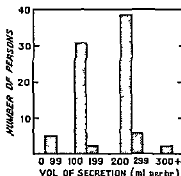
Role of Gastric Acidity in Pathogenesis of Peptic Ulcer A H James and G W Pickering[4] (St Mary s Hosp London) maintained continuous aspiration of gastric contents for 24 hours in 20 patients with duodenal ulcer 23 with gastric ulcer and 20 controls Acid content of the aspirate was determined at frequent intervals Although the mean value for maximal acidity in duodenal ulcer patients was 83 1 m Eq /L and was greater than for the normal subject the difference was not statistically significant The mean minimal acidity during aspiration was more than normal and duration of acidities greater than pH 2 was increased These increases were *statistically significant Acidity rarely fell below pH 5 5 in* either controls or those with duodenal ulcer Curves of intragastric acidity showed that in patients with duodenal ulcer as contrasted with controls there was a higher level of acidity and less conspicuous neutralization after eating and that higher acidities were maintained at night after food had disappeared from the stomach

In patients with gastric ulcer the mean value for maximal acidity (53 5 m Eq /L) was less than normal but the difference was not statistically significant Duration of acidities greater than pH 2 was normal and of acidities less than 5 5 was *increased* significantly *In about two thirds of those with* gastric ulcer intragastric acidity curves fell almost to neutrality during that part of the night when the stomach was empty This gastric *neutralization is apparently due to cessation* of acid secretion

(4) Clin. Sc. 8 181 210 S pt mber 1949

medical histories were obtained on 85 of the original group *Follow up questionnaires* showed no history of dyspepsia in 45 history of minor dyspepsia in 21 history of dyspepsia not suggestive of ulcer in 9 and history of dyspepsia suggestive of ulcer in 10

Results of the original test meal showed that the highest free acidity obtained was practically the same in all groups The average volume of juice secreted by those in whom symptoms suggestive of ulcer subsequently developed was significantly greater than that secreted by the others All dyspepsia suggestive of ulcer occurred in those who had secreted more than 100 ml gastric juice an hour (Fig 111)



Fg 111 —V l m f g t) d d l pm t f b q t mp tom b t b d l m d) p I s g t g p pt l t ppl d l m th dy p p (C t y f D l R t l L t 2 984 985 N 26 1949)

Results indicate that hypersecretion is a cause rather than an effect of peptic ulcer

Nitrogen Balance Studies in Chronic Peptic Ulcer Disease To determine the value of high protein feedings or hyper alimentation regimens in peptic ulcer Thomas S Sappington and Henry L. Bockus[8] (Univ of Pennsylvania) studied pro tein requirements of five patients with chronic uncomplicated ulcer Utilizing an hourly milk feeding program they con ducted nitrogen balance studies and routine blood studies All were on suboptimal protein diets before hospitalization and one had low serum proteins Anemia was not found in any

One patient demonstrated a consistently positive nitrogen balance and was considered to have had a previous nitrogen deficiency therefore an increased protein requirement was in dicated Another patient gave evidence of previous nitrogen deficit and hence increased protein requirement despite incon clusive nitrogen balance data A third patient probably had

(8) A I t. M d 31 271 81 A gu t, 1949

Hydrochloric Acid Test in Diagnosis of Ulcer Georg Gottsegen and Bela Hermann[6] (Budapest) studied the effect of hydrochloric acid and compared the reactions of normal patients and those with ulcers by the following procedure

METHOD —Sixty minutes after a test breakfast the stomach was emptied completely and sodium bicarbonate given through the tube Gastric contents were again removed after 20 minutes and hydro chloric acid was given Reactions were closely observed and to pre vent habitual reactions the drugs were sometimes given in reverse order If pain was caused by the acid the reaction was considered positive

Four hundred patients with normal gastrointestinal tracts were tested first only four of them reacted positively and these exceptions were found to have ulcer craters by x ray In gastric cancer four of six tests gave negative results in the two positive cases there may have been superficial ulcera tion of the neoplasm at the time but this could not be deter mined When the test was given to peptic ulcer patients re actions were positive in one half of the patients with gastric one third with duodenal and all with jejunal ulcers

Subjective objective clinical and roentgenologic findings were studied in an effort to find why there was such a diver gence in ulcer bearing patients X ray findings gastric secre tion length of disease severity of pain and presence of occult bleeding failed to explain the difference in reaction to hydro chloric acid

It seemed significant that when a remission in symptoms occurred the reaction changed from positive to negative suggesting that it was the acute ulcer which reacted with pain In the development of ulcer there is probably a period when there is a tendency to healing and reparative processes occur At such times the base of the ulcer is protected by granula tions and the acid does not produce pain though the anatomic changes persist

It is believed that the hydrochloric test may be an aid in evaluating progress of therapy in peptic ulcers

Gastric Secretion and Subsequent Dyspepsia Follow up Study on 100 normal medical students subjected to histamine test meals 15 years ago was attempted by Richard Doll F Avery Jones and N F Maclagan[7] (London) Subsequent

(6) Ca t oent r log 74 0 279 1948 49
(7) Lancet 2 984 985 N 26 1949

symptomatology and difficulty in localizing the lesion However Smedal states that accurate anatomic diagnosis is possible with the roentgenographic triad which usually indicates ulcer in the sphincter or on its duodenal slope deformity of the base of the cap a poorly differentiated sphincter and antral spasm Figure 112 shows the location of ulcer in the pyloric ring

George A Boylston[1] (Univ of Oregon) analyzed 20 such cases with adequate follow up In 15 ulcer of the ring was

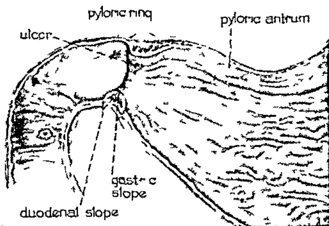


Fig 112 —Pyl g h w g t p l lo t f l (Court y f B yl to G A A h I t M d 84 532 539 O tob 1949)

demonstrated at operation in 5 by x ray alone Prolonged follow up and/or biopsy of each lesion revealed only one malignant ulcer The symptoms averaging 6½ years in duration were typical of peptic ulcer in 11 patients Complaints included gaseous distress after eating in 7 nausea in 10 intermittent obstructive symptoms in 4 and crisis like pain and vomiting in 1 There was no cicatricial pyloric stricture X ray study localized the ulcer in the ring in 12 cases in 5 others craters localized close to but not in the ring on x ray proved at operation to be in the ring Fluoroscopic examination showed antral spasm in eight cases spasm of the bulb in seven and four hour retention of barium in two Of 15 pa

(1) A h I M d 84 532 539 O t be 1949

protein deficiency demonstrating low urinary nitrogen values Others had no protein deficiency as shown by normal nitrogen balance

These results suggest that a daily minimal intake of 15 Gm nitrogen be used for uncomplicated peptic ulcer This is approximately equivalent to 95 Gm protein An hourly 4 oz milk diet is inadequate to meet this protein requirement therefore extra whole protein should be added when the diet is restricted to milk This supplement is easily available in the form of skim milk powder or calcium caseinate

Gastroscopic Appearance of Gastric Mucosa in Peptic Ulcer Recent studies have demonstrated significant differences in the maximal free acidity of gastric secretion between patients with gastric and with duodenal ulcer Maximal free acidity after administration of histamine was low in 21 per cent of the gastric ulcer group it always exceeded 50 clinical units in the duodenal ulcer group William E Ricketts Joseph B Kirsner and Walter L Palmer[9] (Univ of Chicago) studied two consecutive series of patients with duodenal and gastric ulcer respectively to compare the gastric acidity and gastroscopic findings and to seek a possible explanation for the pronounced differences in gastric secretion between the two groups Gastric acidity was measured by the histamine test (0 1 mg/10 kg body weight) Gastroscopic findings were classified as (1) normal (2) atrophy (atrophic gastritis) (3) an irregular cobblestone like mucosa (hypertrophic gastritis) and (4) edema hyperemia and adherent exudate (superficial gastritis)

Analysis demonstrated that peptic ulcer may occur with any type of gastric mucosa the only essential is presence of free hydrochloric acid However there is considerable difference in the appearance of gastric mucosa in gastric and in duodenal ulcer Incidence of atrophy of gastric mucosa is higher in gastric (26 per cent) than in duodenal ulcer (5 per cent) Incidence of hyperplastic mucosa is higher in duodenal (41 per cent) than in gastric ulcer (19 per cent) The frequency of atrophic and inflammatory changes of gastric mucosa in gastric ulcer accounts in most cases for the low output of acid

Ulcer of Pyloric Ring Report of 20 Cases This condition presents a diagnostic problem largely because of a variable

(9) Am J M Sc 217 542 544 May 1949

tients Reasons suggested for the increase included greater use of x rays and an increased tendency to hospitalize ulcer patients particularly as the food situation grew worse In creasing psychic stress inadequate nutrition and growing consumption of tobacco were probably more active as con tributory causes of ulcer in men than in women

During 1912 28 a period previously reviewed by Semb the ratio of perforations in men to those in women was 4 1 From 1929 to 1945 it was 11 1 During these same periods however there was little change in the influence of ulcer lo cation on the tendency to perforation Average age of pa tients with perforations gradually increased with women showing the greater increase This as well as the increase in age of patients without perforation paralleled the increasing age of the general population of Oslo except that the aver age for women with perforations was higher than that of the general population Bjørn Hansen states however that in creased ulcer incidence in older age groups is real it is not due to chronic or protracted ulcers and readmissions The decrease in younger age groups may result from improved living standards for domestic workers higher wages shorter working hours regular meals and improved oral hygiene

Localized Sealed off Perforation in Recurrent Duodenal Ulcer Maurice Feldman[3] (Univ of Maryland) discusses a medical type of sealed off spontaneous pinpoint perforation generally associated with a recurrent active duodenal ulcer with a demonstrable niche defect Severe symptoms and shock are absent Patients are usually ambulatory and there is no free air in the peritoneal cavity Clinical history is character ized by mild and transient attacks not relieved by ordinary treatment methods The patient often complains of persistent pain in the epigastrium somewhat to the right of the midline It lasts longer than usual and tends to become milder and intermittent Later there are persistent soreness and discom fort in the epigastrium sometimes increased by food Vomit ing often occurs during the episode X ray examination re veals a small gas bubble in the subhepatic area above and outside of the duodenal contour Occasionally a small amount of fluid capped with air is seen in the base of the pocket In Feldman s series of five cases no barium entered the pocket

(3) Am J M S 218 378 383 Octobe 1949

tients treated surgically only five reported dyspepsia post operatively On medical management three patients had good results and two had recurrence of symptoms on interrupting therapy

Review of this series and reported cases shows that malig nant ulcer within the pyloric ring is rare However, since no significant symptom complex characterizes these lesions x ray and fluoroscopic examinations are diagnostically important

Investigations of Alterations in Ulcer Clientele in Oslo Municipal Hospital, Ullevaal, over Period 1916-45 Haakon Bjørn Hansen[2] analyzed all cases of peptic ulcer on the medi cal service of this hospital from 1916 to 1941 and with Carl Semb surveyed all cases of perforated peptic ulcer Particu lar attention was paid to the years 1916-25 1935 36 and 1940-41 Average age ratio of men to women was 38 35 years in 1916 25 and 40 47 in 1935 36 and in 1940-41 In men hemor rhage decreased from 74 per cent (75 per cent in women) in 1925 26 of which 60 per cent was gross to 35 per cent (39 per cent in women) in 1935 36 and 1940-41 of which prac tically all was gross There was an increase in the incidence of melena over that of hematemesis coincident with a change in ulcer location from the body of the stomach toward the pylorus and duodenum Average age at the first hemorrhage increased from 38 to 42 years for men and from 35 to 50 for women In both men and women symptoms tended to be of longer duration on both first and readmissions during 1935 36 and 1940-41 than during 1916-25

During 1916-25 x ray studies were made of only 40 per cent of the patients usually at the end of treatment owing to the frequent presence of hemorrhage X rays showed the ratio of duodenal to gastric ulcer in men to be 1 1 and in women 1 1 7 In later years x rays were made before admis sion on practically all patients Thus this ratio for men and women changed to 5 1 and 1 1 in 1935 36 and 1 3 1 and 1 1 7 in 1940-41 The number of men with ulcer and the per cent of total admissions increased greatly the latter from 3 1 per cent in 1915 16 to 10 8 per cent in 1940-41 The increase for women was from 3 per cent to 4 3 per cent over the same period Thereafter an abrupt decline occurred because limited hospital facilities permitted acceptance

(2) Acta med Sc d nav 135 149 171 1949

gestion was obtained In 64 per cent this conformed to a typical ulcer pattern and in 68 per cent symptoms had persisted longer than one year Onset of perforation seemed unrelated to eating habits drinking or smoking or to a particular phase of digestion The moment of perforation was not correlated with position of the patient straining or physical activities The number of perforations occurring in autumn months was considerably lower than in any other season Though there was no significant daily variation in incidence perforation was nearly twice as common in the afternoon and evening as in the morning During the three days before perforation 28 per cent of the patients had no gastric symptoms 37 per cent complained of intermittent abdominal pain 22 per cent of constant pain and 13 per cent had vague complaints such as nausea heartburn and a sense of fulness A physician would in most cases have been unable to anticipate the approaching disaster since no specific pattern of symptoms seemed to lead to perforation

In men perforation of duodenal ulcer was four times as common as perforation of gastric ulcer In women perforation of gastric ulcer occurred twice as often as perforation of duodenal ulcer

[This is an instructive contribution to our knowledge of the most lethal complication of ulcer Of interest is the absence of those factors traditionally regarded as provocative of perforation as well as its unpredictability —Ed.]

Gastric Perforation Clinicopathologic Study John G Shellito and Andrew B Rivers[5] (Mayo Clinic) studied 195 cases of gastric perforation 101 due to benign and 94 to malignant lesions to discover differences which would facilitate a preoperative diagnosis The average age of patients in both groups was 52 7 years the ratio of males to females was 6 8 1 in cases of perforated benign ulcers and 3 9 1 in malignant perforations Free acute perforations occurred in only 4 3 per cent of malignant lesions and in 5 9 per cent of benign the greatest number in this series were walled off and well localized by natural peritoneal barriers

A typical ulcer history was obtained in 61 4 per cent of patients with perforated benign lesions but in only 28 6 per cent with malignant perforations An atypical but suggestive

(5) G : oent logy 12 919 933 J e, 1949

Because of the minimal amount of air which escapes from the pinpoint perforation the subhepatic gas bubble is best demonstrated by the spot film compression technic with the patient in an erect position (Figs 113 and 114) This small amount of air and sometimes fluid usually disappears within a few weeks of treatment

This form of walled off perforation probably occurs more *often than has been suspected It should be looked for in all*



Fig 113 (left) —F lm made n r t pos t n w th pot film c mp es o show g ma k dly d form d duod al bulb w th l ge a r b bble abo e d od n m (r rows) N te fl tte ed ba e f a r pocket due to mall mo nt of fl d
F g 114 (ght) —Same cas F lm mad in rec mbent pro e po tion w thout mp s n No g pocket c n be dem t at d
(Courtesy of Feldman M. Am. J M S 218 378 383 October 1949)

ambulatory patients with recurrent duodenal ulcer who present symptoms which are more severe than those usually experienced

Factors Associated with Perforation in Peptic Ulcer have been studied by Christopher Strang and I O B Spencer[4] (Newcastle upon Tyne) Of the 189 patients with perforated peptic ulcer reviewed all but 12 were men giving a much greater male to female ratio than is generally true for peptic ulcer Perforation is rare under age 20 but has a fairly even distribution in other decades Jobs entailing a moderate amount of responsibility were held by 18 5 per cent of the ulcer patients whereas only 5 per cent of the hospital population held employment with a similar amount of responsibility

In 91 per cent of the patients a history of previous indi

(4) B t M J 1 873 876 Ap 15 1950

in the individual patient pathologic examination of the lesion is the only certain procedure

[The profession is indebted to the late Andrew B Rivers for his several investigations with respect to pain and its characteristics in primary anastomotic and recurrent postoperative ulcer The significance of its location the radiation character probable nerve pathways and differential features of visceral and somatic elements are problems which he helped so much to clarify His description of the symptom complex of duodenal ulcer perforating into the pancreas is a classic (1948 YEAR BOOK OF GENERAL MEDICINE, p 665) —Ed]

Management of Patients with Bleeding from Upper Gastrointestinal Tract with Buffer and Thrombin Solution Byrne M Daly Charles G Johnston and Grover C Penberthy[6] (Wayne Univ) developed the buffer and thrombin method *during study of 100 consecutive cases and report the procedure* found most effective

METHOD —A Levin tube passed through the nose into the stomach is washed out with buffer or saline solution and 50 cc of M/7 phosphate buffer then introduced into the stomach and left five minutes An additional 50 cc phosphate buffer is introduced and with it 10 000 units of topical thrombin The tube is clamped 30 minutes during which blood studies are made and if blood loss appears serious a transfusion is given After 30 minutes the clamp is removed from the tube and slow gentle suction is applied by mean of a pump with a valve mechanism that permits low suction not to exceed 1 ft water The material removed is observed through a glass connector If bleeding has stopped the material usually is finely *granular and light colored if bleeding continues fresh blood stained* material can be seen in the tube If there is no bleeding 50 cc buffer solution is introduced every half hour allowed to remain a half hour and then aspirated The buffer may be given by slow drip This process is carried on for several days If bleeding continue the process is repeated If the bleeding appears uncontrolled by thrombin administration other measures must be resorted to The phosphate buffer is made by mixing 20 4 Gm disodium phosphate in 1 L water with 1 95 Gm dihydrogen potassium phosphate in 100 cc water pH is 7 6

Bleeding in 87 patients was controlled by use of thrombin buffer alone In eight others the hemorrhage was controlled but recurred in three it could again be controlled but for five operation seemed the safer procedure In four patients bleeding recurred after having been controlled with thrombin and further treatment was ineffective One other patient died of massive hemorrhage in which bleeding was at no time controlled

Though the thrombin and buffer method is useful in con

(6) Ann. S g 129 832 839 J ne. 1949

story was given by 23 8 per cent of patients with benign and 36 2 per cent with carcinomatous perforation and a history not typical of ulcer was obtained from 13 8 per cent of patients with benign lesions and 24 5 per cent with malignancies Slow insidious onset of symptoms was the rule with perforation causing exaggeration of symptoms Perforation of benign ulcers seemed to be associated with more definite symptoms whereas malignant lesions progressed faster All acute perforations gave a somewhat typical history of pre existing ulcer A mass was palpable in only 25 5 per cent of malignant lesions this finding should indicate that the lesion is malignant and rather far advanced Weight loss, usually considered of prime importance in diagnosis of malignant lesions occurred here more often in benign lesions Hypoacidity tended to occur in malignant perforations and hyperacidity in benign although normal gastric acidity was often found in both groups A rigid abdomen was found only in patients with acute perforations

Most gastric perforations occurred on the posterior wall of the lesser curvature Carcinomatous lesions tended to locate toward the pylorus and benign lesions near the angle Location of the lesion on the anterior wall and greater curvature is not considered a specific indication of malignancy Pancreatic involvement occurred in 81 per cent of benign perforations and in only 51 per cent of malignancies Carcinomatous lesions had a mean diameter of 2 52 cm compared to 1 85 cm for benign perforations suggesting that at operation lesions greater than 2 cm should be considered malignant until proved otherwise Duodenal ulcer was associated with benign gastric ulcer in 13 per cent of patients with sarcoma of the stomach in two of three instances but in no instance with adenocarcinoma In 3 per cent of benign perforating lesions an additional benign gastric lesion was found An additional malignant lesion occurred in 2 1 per cent of malignant perforations

Gastric resection is the operation of choice in walled off perforation malignant or benign as well as in free perforation In the latter case if immediate resection is not feasible primary closure followed later by gastric resection is recommended A rigid abdomen associated with gastric ulcer should be considered an indication for immediate surgery Since no significant features differentiate benign from malignant lesions

blood and to raise the red cell count above 3 500 000 Since it was impossible to foretell if a patient would require surgery to stop bleeding early operation was performed (1) on all patients over age 40 with bleeding from peptic ulcer 48 hours in duration (2) on those with appreciable recurrence and (3) on diagnosis of extensive penetration or a complicating disease Urgent operation was successfully performed in nine cases after definite diagnosis of ulcer The authors estimate that under conservative therapy mortality would have been 50 per cent of the operated group Thus an earlier and more radical surgical approach to bleeding ulcer complicated by arteriosclerosis cirrhosis portal hypertension diabetes or penetration resulted in a lower mortality

Lethality Rate of Hematemesis and Melena Treated Nonoperatively (Meulengracht s Regimen) and Criteria for Surgical Intervention in Bleeding Peptic Ulcer Jørgen Pedersen[8] (Copenhagen) reviewed about 850 cases of bleeding peptic ulcer and ulcer disease treated by Meulengracht s principles during a 10 year period The gross mortality rate was about 3 5 per cent in about 2 per cent death was due to exsanguination Pedersen then analyzed (1) all fatal cases of peptic ulcer hemorrhage in patients aged 40 and over (2) all cases of survivors of hematemesis or melena observed in the hospital who were over 40 had a peptic ulcer demonstrated by x ray or on operation and in whom the lowest hemoglobin was less than 80 per cent

There was no death from melena below age 60 The few patients dying from or with bleeding peptic ulcer without hematemesis were those suffering from mechanical obstructions of the stomach and duodenum In these instances the melena was considered a masked hematemesis In addition this group contained patients so debilitated they were unable to vomit the blood In patients reported to have had hematemesis before hospitalization and melena after the mortality was comparable to that for melena alone Exsanguinated patients of these two groups are considered cases for the Meulengracht regimen

Seventy per cent of all fatalities had hematemesis after hospitalization Of those dying from exsanguination 90 per cent had hematemesis in the hospital In the age group 40-49

(8) Gastroenterology 12 597 616 Ap 1 1949

trolling hemorrhage from the upper gastrointestinal tract, i should not be considered a sole form of therapy When it is ineffective early operation is necessary The method in conjunction with the Patton tube is useful in determining whether a patient is bleeding from the esophagus or from below the cardia of the stomach

Combined Medical and Surgical Management of Upper Gastrointestinal Hemorrhage is the most efficient treatment according to Thomas A Warthin Richard Warren and Egon G Wissing[7] (Veterans Admin Hosp West Roxbury, Mass) Of 86 cases of massive hemorrhage 56 (65 per cent) were due to peptic ulcer and 30 to esophageal varices gastritis or undetermined causes Among 14 cases in which no cause was found only 3 had histories suggestive of ulcer Of 11 deaths (mortality 12 8 per cent) 2 occurred in the ulcer group and 9 in the nonulcer Hemorrhage was the primary cause of death in only 6 of the 11 cases 3 died of liver failure, 1 of peritonitis and malnutrition and 1 of terminal carcinoma of the stomach Ten of the 11 deaths occurred in patients who had either hepatic cirrhosis or portal hypertension as a primary or secondary diagnosis In three patients who were not bleeding frankly from esophageal varices the source of hemorrhage was gastric ulcer in two and undetermined in one. Thus it appears that the prognosis is poorer in those in whom bleeding is due to or complicated by factors interfering with nutrition or the normal state of the gastrointestinal blood vessels

The ability to make a differential diagnosis on clinical grounds alone at time of active bleeding was limited Two aids in diagnosis of peptic ulcer were previous diagnosis of ulcer and presence of pain during bleeding Pain antecedent to bleeding proved unreliable Emergency x rays were done on patients with persistent or recurrent bleeding who could be operated on quickly if an ulcer diagnosis were made and on patients with recurrent bleeding of undetermined origin Study of films showed that a minimal degree of deformity of the duodenal bulb during emergency was not positive evidence of ulcer

In addition to conservative medical treatment free use was made of transfusions to prevent shock to replace lost

(7) New England J Med. 241 473 478 Sept. 29 1949

blood and to raise the red cell count above 3 500 000 Since it was impossible to foretell if a patient would require surgery to stop bleeding early operation was performed (1) on all patients over age 40 with bleeding from peptic ulcer 48 hours in duration (2) on those with appreciable recurrence and (3) on diagnosis of extensive penetration or a complicating disease Urgent operation was successfully performed in nine cases after definite diagnosis of ulcer The authors estimate that under conservative therapy mortality would have been 50 per cent of the operated group Thus an earlier and more radical surgical approach to bleeding ulcer complicated by arteriosclerosis cirrhosis portal hypertension diabetes or penetration resulted in a lower mortality

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(8) Ga t oe t Jogr 22 597 616 Ap 1 1949

the mortality rate was not high enough to indicate surgery for the entire group However in patients over 50, mortality from exsanguination was 30 per cent The following criteria were therefore tentatively proposed for surgical intervention in peptic ulcer hemorrhage age 50 or over hematemesis in the hospital and proved peptic ulcer Of 40 patients in this group only 32 were operable Of these eight died during conservative treatment (25 per cent) In operable cases skilful surgery might be performed with only a 10 per cent mortality When specialized surgeons are available and surgery is not contraindicated *patients of this group should be operated on following the first hematemesis in the hospital*

[The significance of advanced age as the most important factor in death from hemorrhage is again emphasized by Pedersen Of interest too is the seriousness of hematemesis in contrast to melena the former implying rapid bleeding in his opinion —Ed]

Peptic Ulcer in Man Status of Ulcer Therapy is reviewed by S P Bralow H Kroll M Spellberg and H Necheles[9] (Michael Reese Hosp) Although it is generally accepted that peptic ulcer is a local weakness of the mucosa of the prepyloric segment or first portion of the duodenum precipitated and aggravated by acid pepsin secretion the evidence supporting this view is incomplete The ulceration may be a manifestation of a systemic neurocirculatory disorder Therefore treatment designed to neutralize acid content or inhibit pepsin activity must be considered merely symptomatic therapy which if properly used may or may not decrease the rate of recurrence

Sippy powders and other absorbable alkalis are unsatisfactory because of the incidence of alkalosis and of secondary acid secretion The favorable effects of milk protein cream and alkali are outweighed by the increased secretion of gastric juice frequent simulation of the reflex phase of gastric secretion repeated feedings and late stimulating effects of fat and alkali after absorption Among nonsystemic alkalis calcium carbonate magnesium carbonate and magnesium oxide or trisilicate are most useful but present disadvantages The calcium ion is constipating the magnesium ion produces laxation and carbonates are absorbed in sufficient amounts to produce alkalosis and acid rebound

Colloidal aluminum preparations which are at pre ent

(9) Am J Dig st. Dis. 17 86 92 March 1950

widely used are clinically effective but produce constipation and relatively rapid elimination from the stomach These preparations may absorb phosphate and delay emptying time of the stomach The wide variation in carbonate content among the various brands may partly explain the difference in speed of action

The use of protein hydrolysate is directed at secondary nutritional deficiencies rather than at the cause of the ulcer Enterogastrone and sodium lauryl sulfate have not been proved superior to more conservative agents Hog s mucin would appear to be best physiologically since gastric mucus protects smoothes and lubricates the mucosa and acts as a natural antacid Its unpleasantness orally and the belief that its clinical effects are not impressive have led to a search for a synthetic gastric mucin which would comprise the theoretical ideal for an antacid Sodium carboxymethylcellulose has proved satisfactory because it is bland adheres to the gastroduodenal mucosa is unabsorbable not constipating and has a sufficient neutralizing ability

[This is a judicial appraisal of current treatment for ulcer especially from the standpoint of antacids Antacids leave much to be desired because they leave the stomach rapidly and their admixture with the gastric contents is often incomplete This is especially true of the less soluble antacids now in vogue The consequent resort to measures to prevent or reduce the amount of acid secreted to date has not been signally successful However progress is slowly being made in this direction and we look forward to the final report concerning sodium carboxymethylcellulose —Ed]

Continuous Drip Treatment of Peptic Ulcer, according to A M Clark[1] (Worcester England) requires minimal attention from the nursing staff can be used by the patient at home and is well tolerated Indications for the drip method are active ulcer recent hematemesis or melena and poor general condition

METHOD —The drip is given through a Ryle tube passed through the patient s mouth so that a point 14 in from the tip lies opposite the teeth The best solution is fresh milk citrated with 40 gr sodium citrate/pt delivered at a rate of 100 oz /24 hours Next most satisfactory is magnesium bicarbonate in 1 3 dilution with water of the B P solution delivered at a rate of 80 oz /24 hours Since the latter may have a laxative effect 15 minims of tincture of opium should be added to the drip reservoir twice daily In cases of anemia ferrous sulfate is given All patients should receive 50 mg ascorbic acid daily Those on the milk drip are given 1 gr phenobarbital twice

(1) Lan t 1 435 438 M 11 1950

daily The more seriously ill patients are confined strictly to bed on a milk drip without additional nourishment Others may have a routine gastric diet which excludes gross roughage chemical irritants and fried foods During the meal they may remove the tube The drip is continued for three weeks then after an additional week in bed, the symptom free patient may be allowed up gradually If relapse is expected the patient is advised to set up a drip at home for use in the nigh or continuously over the weekend

Although in reacting with hydrochloric acid magnesium bicarbonate gives off carbon dioxide no case of alkalosis has been detected clinically or by chemical analysis

Of 29 patients with peptic ulcer demonstrable by x rays 19 had no evidence of ulcer 1 16 weeks after the drip ended Only one of this group was not symptom free

Modus Operandi of Carminatives Therapeutic Value of Garlic in Functional Gastrointestinal Disorders Carminatives defined as aromatic and pungent drugs used in flatulence and colic to expel gas and to diminish griping pains act by diminishing gastric movements and tension and by relaxing sphincters The uses and action of dehydrated garlic as a carminative were investigated by x ray and clinical studies conducted by Frederic Damrau and Edgar A Ferguson[2] (New York City)

In 25 patients with gastrointestinal complaints barium x rays were taken with and without administration of garlic to determine the effect of garlic on gastric and intestinal motility Six 4 75 gr tablets were given two with the barium meal two after two hours and two after four hours The gastric barium residue was larger with use of garlic indicating a sedative and delaying action on peristalsis

In 29 patients complaining of postprandial heaviness belching flatulence gas colic and nausea two garlic tablets were administered twice daily after lunch and dinner for two weeks Severity of symptoms was numerically rated to determine degree of benefit after treatment Postprandial heaviness regarded as consciousness of peristalsis was completely relieved in 15 patients partially relieved in 6 and not relieved in 4 Complete relief from belching occurred in 13 patients partial relief in 9 and no relief in 3 In 20 of 25 patients flatulence was relieved Complete or partial relief was obtained

(2) Re G troent I 16 411 419 May 1949

in 21 of 24 patients with colic and in 6 of 8 patients with nausea After two weeks of medication roentgenograms of these 29 patients showed delayed peristalsis

These results indicate that unidentified principles in garlic exert a sedative action on the Meissner plexus in the stomach and small intestines and probably on the Auerbach plexus causing a relaxation of tone and motility of the gastrointestinal tract The descriptive name gastroenteric allichalone (from *allium* garlic *chalone* to relax) was applied to these principles

Influence of Smoking on Management of Peptic Ulcer Patient Roger C Batterman and Irving Ehrenfeld[3] (New York Univ) considered two phases of this problem (1) the influence of tobacco smoking measured by the effectiveness of antacid therapy and incidence of acute exacerbations (2) the influence of smoking partially denicotinized tobacco on the peptic ulcer syndrome Of 108 patients studied 39 were non smokers and 26 discontinued smoking on first seeking treatment Excellent response to antacids was obtained in these groups with the incidence of exacerbations reduced to 11 5 and 17 5 per cent respectively Patients who continued to smoke regular tobacco showed only a 47 per cent effective response to antacid therapy with a 53 per cent incidence of exacerbations

Among the smokers 28 who had persistent symptoms and whose dietary and antacid response was poor were supplied with processed cigarettes (nicotine content averaging 0 85 per cent in contrast to 1 5 2 5 per cent in standard brands) Immediate improvement resulted in 78 6 per cent Eleven patients had complete relief from symptoms notably heartburn and epigastric pain Among those with moderate improvement symptoms persisted but were of undisturbing character Only 28 6 per cent of this group had acute exacerbations Reinstitution of camouflaged regular tobacco in 18 patients who had responded well to processed cigarettes caused a decreased response to antacids and a corresponding increase in exacerbations

The authors conclude from a comprehensive survey of the physiology and pharmacology of tobacco smoking that nicotine is probably an etiologic factor in gastrointestinal disor

(3) G troe t logy 12 575 585 Ap l 1949

ders and that tobacco smoking is detrimental to the peptic ulcer patient

Acid Neutralizing Power of Several Protein Hydrolysates and Other Substances Used in Ulcer Therapy Sidney M Samis and Franklin Hollander[4] (Mt Sinai Hosp New York City) compared the buffering action of four commercial protein hydrolysates and of unhydrolyzed protein alumina gel sodium bicarbonate whole fresh milk and other common antacids Buffer curves were determined by electrometric titrations with N/10 HCl under standardized conditions using a glass electrode The buffering power between initial pH and pH 3 5 was estimated by interpolation from the titration curves (pH 3 5 used as the boundary value between free and combined gastric acidities)

Three of the four protein hydrolvsates showed a relatively high neutralizing power down to pH 3 5 sufficient to be effective antacids when given by mouth in daily dosage of 300 Gm (the minimum daily amount usually administered by Co Tui) Whereas 300 Gm of the most effective hydrolysate was capable of neutralizing 5 500 cc of N/10 HCl in vitro the same amount of acid required 45 Gm $NaHCO_3$ to bring the pH to 3 5 On a daily basis protein hydrolysates proved superior to alumina gel None of the other substances investigated could compare even to alumina gel in acid neutralizing action The authors concluded that the acid neutralizing function as well as the nutritive value of protein hydrolysates is highly important when these preparations are used in oral treatment of peptic ulcer

[One of the most encouraging reports it confirms Levy and Siler s observations (1942) regarding buffering action of a pancreatic hydrolysate of casein (amigen®) A pancreatic hydrolysate of lactalbumin (lactamin®) and Squibb s protein hydrolysate (pancreatic hydrolysate of casein) shared honors with amigen® in the study by Samis and Hollander —Ed]

Antipeptic and Antacid Therapy With Special Reference to Adsorbent Complexes of Calcium and Magnesium Phosphates Etiology of persistent hyperchlorhydria is obscure Only in a few cases can hyperchlorhydria be attributed to alcohol coffe or condiments Treatment must therefore be directed to neutralization of acid or to control of gland cell and nerve ending mechanisms

(4) Gastroenterology 12 665 670 Apr 1 1949

Nathan Mutch[5] (Guy s Hosp London) reviews methods of diminishing gastric acidity and discusses the antipeptic action of antacids with particular reference to calcium and magnesium phosphate compounds The most important mineral antacids are magnesium oxide carbonate phosphate trisilicate and basic trisilicate calcium carbonate phosphate and silicate aluminum hydroxide basic carbonate phosphate aminoacetate and aluminum sodium silicate Except for magnesium oxide basic magnesium trisilicate and sodium bicarbonate alkalinizing agents to be used with caution these reduce HCl concentration to various extents within desirable clinical range In all there is wide discrepancy between estimated acid secretion and amount of antacid necessary for neutral interaction

The digestive action of pepsin is thought to have an erosive effect on the peptic ulcer base This effect can be prevented by several means (1) Overneutralization to pH 5 or more abolishes pepsin activity However it is not usually feasible to reduce acidity continuously to this level with antacids (2) Pepsin can be destroyed by aluminum salts (3) Adsorption of pepsin on kaolin and silica gel reduces its activity but does not destroy its digestive function (4) Magnesium trisilicate and basic and, activated calcium and magnesium phosphates also adsorb pepsin forming nonproteolytic complexes

Activated phosphates are complexes of hydrated silica and tribasic calcium or magnesium phosphate they are insoluble in water but react with HCl to form soluble chlorides free phosphoric acid and hydrated silica residue These silica complexes have greater adsorptive action than any dried free silica gel available In 10 patients with chronic peptic ulcer and 13 new patients activated phosphates were given as the sole antacid in doses of 2 drachms every two hours with excellent clinical results They also proved adequate in test meal fractional studies

Effect of Urecholine® on Stomach Intestine and Urinary Bladder was investigated by I F Stein Jr and Karl A Meyer[6] (Cook County Hosp) A balloon was placed in the vagotomized stomach of each of 12 patients and kymographic

(5) *La t 1 859 8/3 M y 21 1949*
(6) J A M A 140 5 2 5 5 J 11 1949

tracings were made after administration of urecholine* In each of three patients 5 mg urecholine* given subcutaneously increased gastric motility in 5 10 minutes (Fig 115) In eight patients 10 mg given orally produced moderate to pronounced increase in gastric motility in 30 minutes to 1½ hours lasting 30 minutes to 3 hours Sublingual administration of 10 mg caused only slightly increased gastric motility in one patient whereas 25 mg produced adequate stimulation Clinical observations on 10 additional patients with symptoms of gastric retention after vagotomy showed that 20 30 mg of

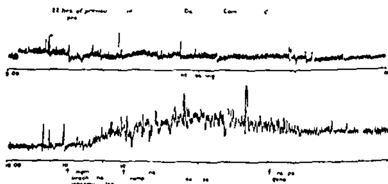


Fig 115—Effect of urecholine* on gastric motility (Courtesy of St I F Jr and Meyer K A J A M A 140 522 5 5 June 11 1949)

the drug three times daily before meals gave satisfactory results in all Urecholine* 10 20 mg given orally for 10 20 days after gastric resection without vagotomy relieved four of five patients with symptoms of poor gastric emptying or retention The patient who was not relieved was found at reoperation to have a kink which obstructed the gastrojejunal anastomosis

Of 20 patients with adynamic ileus 13 passed gas and feces 10 minutes to 2 hours after administration of urecholine* Those with severe ileus received 5 mg subcutaneously followed three hours later by 25 30 mg orally or sublingually The dosage was repeated four times a day if necessary Oral administration of 20 30 mg urecholine* usually relieved mild postoperative abdominal distention In five patients gradual improvement occurred in two to three days in two a single dose of urecholine* failed to relieve distention

Of 18 patients with postoperative urinary retention 15 voided 3 10 minutes after subcutaneous injection of 5 mg urecholine* The drug gave relief from urinary retention in one of two patients with transverse myelitis and in one with cord bladder In a second patient with cord bladder evacuation of the bladder was completely controlled by urecholine* In four patients with urinary retention urecholine* promptly increased intravesical pressure to a maximum in 3 10 minutes The catheter through which manometric readings were taken was removed 10 minutes after the drug was given Each patient voided spontaneously in one minute

Theoretical contraindications to use of urecholine* include unhealed gastrointestinal anastomosis peritonitis mechanical intestinal obstruction pregnancy and asthma

Results show that urecholine* is a potent parasympathomimetic drug of low toxicity which stimulates gastric motility in the normally innervated and in the vagotomized stomach It is of definite value in treatment of both adynamic ileus and postoperative urinary retention although its effective use in cord bladder must still be determined

[This is an encouraging report, but one does occasionally meet with disappointing r sults with th s drug in the treatment of postoperative mor b d physiologic conditions —Ed]

Dry Feedings in Gastric Motor Delay Jerome E Cook and Edward C Malewitz[7] (Jewish Hosp St Louis) evaluated use of dry diets with all fluids administered parenterally for treatment of gastric or duodenal ulcers associated with gastric motor delay Only patients who had failed to improve on conventional Sippy or Meulengracht diets were included The diet consisted mainly of finely divided hard boiled eggs dry cottage cheese cooked cereal without added cream crackers minced chicken mashed potatoes and rice Butter was added to the cereal foods The usual antispasmodics antacids and sedatives were continued Initially nightly aspirations of gastric residuals were done

Gratifying results were obtained in several cases one of which is included here

Man 67 had hunger pains for five years and had lost 80 lb despite the usual Sippy regimen Constant vomiting had been present for six weeks X rays showed over 50 per cent gastric retention in five hours and evidence suggestive of duodenal ulcer On a Sippy

(7) Am J Dg t D 16 2 2 4 J 1949

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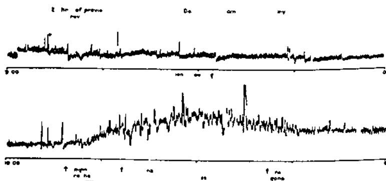


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Of 20 patients with adynamic ileus 13 passed gas and feces 10 minutes to 2 hours after administration of urecholine® Those with severe ileus received 5 mg subcutaneously followed three hours later by 25 30 mg orally or sublingually The dosage was repeated four times a day if necessary Oral administration of 20 30 mg urecholine® usually relieved mild postoperative abdominal distention In five patients gradual improvement occurred in two to three days in two a single dose of urecholine® failed to relieve distention

that among 31 per cent of patients reporting a favorable course only 15 3 per cent remained entirely free from ulcer distress In 19 per cent slight but frequent recurrence of trouble was reported Of the 40 per cent who had a serious course 3 9 per cent died of peptic ulcer and the remainder had definite relapses leading to further treatment or operation Of the deaths attributed to ulcer 74 per cent occurred during the year following treatment and 2/3 were associated with operations Mortality was greatest among older patients The prognosis seemed somewhat more favorable for gastric ulcer patients than for those with duodenal ulcers 21 9 per cent of the former remaining totally free from distress compared with 12 7 per cent of the latter Duodenal ulcer however was associated with a lower mortality rate Duodenal ulcer patients with a history of more than five years showed a pronounced tendency to relapse (87 5 per cent) particularly those who had undergone previous treatment Gastric ulcers showed a greater tendency to hemorrhage with the risk greatest when hemorrhage had previously occurred The mortality for hemorrhage in the entire group was 1 6 per cent for perforation 1 2 per cent

During the observation period 135 patients were operated on 68 9 per cent with favorable results Because in gastric surgery there is now a low primary operative mortality the authors believe most peptic ulcers can be treated surgically particularly those refractory to relapse prophylaxis

Peptic Ulcer Cases Reviewed after 10 Years Effect of Medical Treatment and Indications for Gastrectomy Laurence Martin and Ninian Lewis[9] (Addenbrooke s Hosp Cambridge) believe that the only way of assessing value of treatment of chronic disease such as peptic ulcer is by a long term follow up survey which shows how the natural course has been influenced They interviewed and examined 195 patients (Table 1) most of whom were treated medically A few were in need of operation because of perforation Cases of anastomotic ulcer were included under primary ulcer Deaths as a direct result of ulcer are listed in Table 2 and deaths from other causes are listed in Table 3

There were 123 gastric and 62 duodenal cases Fifty per cent of the gastric and 39 per cent of the duodenal ulcers were

(9) La cet 2 1115 1120 D 17 1949

diet with antispasmodics antacids and sedation vomiting continued and nocturnal gastric residuals of 450 cc were aspirated Immediate relief followed use of dry feedings and intravenous fluids Diminution in nightly residuals occurred and the patient showed a weight gain after five days Gastric retention decreased to 25 per cent in five hours and fluids by mouth were then permitted

The mechanical factor of peristaltic inhibition by fluids but not by solids and the psychologic value of change from liquid to solid food as well as the added caloric value of concentrated food were considered of importance in the success of therapy The smaller volume of feedings may help a dilated stomach regain tonus Complete withdrawal of oral feeding may not be necessary or advantageous in pyloric obstruction dry feedings although not a treatment of choice in peptic ulcer or other lesions may satisfactorily tide a patient over a period of gross gastric retention

[Empirically perhaps but for years my surgical colleagues have resorted to a dry diet under the circumstances mentioned usually with salutary effect The necessary fluids were administered orally 2-4 hours after feedings or parenterally when circumstances required it —Ed]

Postinvestigation of 687 Medically Treated Cases of Peptic Ulcer has led Haqvin Malmros and Tor Hiertonn[8] (*Orebro Central Hosp Sweden*) to conclude that ulcer disease has a poor prognosis Only cases in which diagnosis had been verified by x ray and which had been observed for 7 10 years after treatment were included Of the 687 patients 495 had duodenal and 192 gastric ulcers On admission for treatment 18 per cent had severe manifest hemorrhage associated with gastric ulcer in 50 patients with duodenal in 75 In 5 2 per cent previous operation for perforation had been done

Ulcer treatment included bed rest in the hospital for three to four weeks and the following diet liquid or semi liquid diet the first week pureed the second and pureed plus easily digested solids the third Abundant calories were supplied throughout treatment even in hemorrhagic cases A mixture of magnesium subcarbonate bismuth subsalicylate and extract of belladonna was given three to five times daily Most patients also received phenobarbital 0 025 Gm three to four times daily

Preliminary result of treatment was good 93 5 per cent of patients showing no crater on x ray Postinvestigation results however based on the history and hospital records showed

(8) Acta m d S d 133 229 252 1949

that, among 31 per cent of patients reporting a favorable course, only 15.3 per cent remained entirely free from ulcer distress. In 19 per cent slight but frequent recurrence of trouble was reported. Of the 40 per cent who had a serious course, 3.9 per cent died of peptic ulcer and the remainder had definite relapses leading to further treatment or operation. Of the deaths attributed to ulcer 74 per cent occurred during the year following treatment and 2.3 were associated with operations. Mortality was greatest among older patients. The prognosis seemed somewhat more favorable for gastric ulcer patients than for those with duodenal ulcers, 21.9 per cent of the former remaining totally free from distress compared with 12.7 per cent of the latter. Duodenal ulcer, however, was associated with a lower mortality rate. Duodenal ulcer patients with a history of more than five years showed a pronounced tendency to relapse (87.5 per cent), particularly those who had undergone previous treatment. Gastric ulcer showed a greater tendency to hemorrhage, with the risk greatest when hemorrhage had previously occurred. The mortality for hemorrhage in the entire group was 1.6 per cent, for perforation 1.2 per cent.

During the observation period 13[illegible] patients were operated on, 68.9 per cent with favorable results. Because in gastric surgery there is now a low primary operative mortality, the authors believe most peptic ulcers can be treated surgically, particularly those refractory to relapse prophylaxis.

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(3) Lancet 2: 111[illegible]-11[illegible], Dec. 1[illegible], 1949.

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(8) A t m d S nd v 133 29 25 1949

chance of hemorrhage was about 1 3 for all gastric and duodenal ulcers and the chance of dying of it was 1 25 About 80 85 per cent of the patients with bleeding were aged 40 70 About 60 per cent of patients with 10 years or more of activity had hemorrhage Mortality from this complication was highest in patients over 50 There was a 1 3 chance of perforation for all cases either within 5 years of onset or after 10 years with only a small incidence in the intervening period About 80 per cent of gastric perforations occurred between ages 40 and 70 compared with 60 5 per cent of duodenal perforations

Gastrectomy should not be recommended if a reasonable chance exists that an ulcer will heal Medical treatment of gastric ulcer is justified by the fact that about 30 per cent in this series healed without surgery It should be remembered that the mortality from gastroduodenal hemorrhage is influenced greatly by the age of the patient and scarcely at all by the length of ulcer history Each case must be judged on individual circumstances but in general gastrectomy is advocated for peptic ulcer after 10 years duration or whenever possible by age 50 If this were carried out invalidism complications and deaths from chronic peptic ulcer would be greatly diminished

[Reports of similar nature from sources at home and abroad are disappointing and leave little room for complacency or self satisfaction on the part of physician and specialist —Ed]

Immediate Results of Partial Gastrectomy for Peptic Ulcer In 101 cases analyzed by B B Milstein[1] (Univ College Hosp London) partial gastrectomies were performed for peptic ulcer without pyloric stenosis in 72 cases for non malignant organic pyloric stenosis in 28 and for hypertrophic pyloric stenosis in 1 Indications for surgery included intractability recurrence repeated hematemeses pyloric obstruction hemorrhage suspected cancer and hour glass contracture Many patients had undergone lengthy medical treatment No patients were refused operation because of age or the presence of complications Except in acute hemorrhage all complications related to the ulcer were treated before surgery Suspected activity of the ulcer was treated by at least three weeks bed rest and a suitable gastric diet

The following lesions were present at operation 38 gas

(1) La et 1 514 517 M 6 1949

inactive following various treatments A history of characteristic ulcer dyspepsia during the preceding five years was considered activity Of the 96 gastric and 43 duodenal cases treated medically 44 per cent of the former and 32 5 per cent of the latter were inactive In most of the remainder perseverance with a regular or occasional regimen of diet and alkali had little effect on the healing of the ulcers or the incidence

TABLE 1

T E OF ULC	D	TR CED	UNT ED	T T L
Gastric	97	123	11	231
Duodenal	35	62	8	105
Gastric + duodenal	10	10		20
Total	142	195	19	356

TABLE 2 —DEATHS AS DIRECT RESULT OF ULCER

CAU	G ST IC	DUO L	C TRIC + DU ENAL	T T I
Hemorrhage	9	5	1	15
Perforation + operation	21	7	2	30
Perforation no operation	5	2	–	7
After gastrectomy	6	1	2	9
After gastroenterostomy	3	3		6
After other operations for ulcer	5	2	1	8
Total	49	20	6	75

TABLE 3 —DEATHS FROM OTHER CAUSES

TY E O ULC	ULCE ACT	ULCER INACT E	ACTIVIT UNKNOWN	TOTA
Gastric	16	9	17	42
Duodenal	6	1	8	15
Gastric + duodenal	1	...	3	4
Total	23	10	28	61

of complications and consequently did not influence the natural course of the disease For gastric ulcer patients there was a significantly greater chance of healing and inactivity 10 years later if there was a short rather than a long history at time of hospitalization In both groups successful medical treatment was unlikely in more than 50 per cent of those admitted to the hospital

The generally accepted indications for gastrectomy are intractable chronicity hemorrhage perforation and malignant change Gastrectomy should be considered in all patients with peptic ulcers of 10 years duration for beyond this point the chances of rapid healing diminish In this series the

and the avoidance of secondary operations for obstruction were attributed to preoperative rest strict suture technic and routine postoperative gastric suction The author recognizes that the strict suture technics by prolonging the operation increase the risk of contamination

Postoperative complications occurred in 51 per cent of all operations although the incidence dropped 39 per cent in the later cases Chemotherapy early ambulation pre and post operative exercises were possible contributing factors Wound infection chiefly staphylococcic was the outstanding single complication Local application of penicillin to wound layers *during closure and use of stainless steel sutures are recom* mended for prevention of such persistent infections

Symptomatology and Diagnosis of Gastric Cancer John S LaDue Paul J Murison Gordon McNeer and George T Pack (Memorial Hosp New York City) studied the records of 1 117 patients with gastric cancer to determine whether any correlation existed between duration and signs and symp toms and resectability rate The incidence of resectability in patients with gastric cancer was 39 8 per cent and the rate of five year survival varied from 42 8 per cent for patients with out nodal metastases to 24 2 per cent for those in whom disease was not confined to the stomach When cancer involved the cardia resectability rate was 59 per cent

The frequency and multiplicity of symptoms in patients with inoperable and operable gastric cancer was essentially the same except that dysphagia was twice as common with inoperable carcinoma In order of frequency symptoms were loss of weight (83 5 per cent) pain vomiting bowel dis turbances anorexia dysphagia nausea weakness eructa tion hematemesis and rapid satiation (4 6 per cent) Weight loss over 41 lb was usually associated with inoperable gastric cancer The more rapid the weight loss the more striking are hepatic dysfunction hypoproteinemia inanition and other metabolic deficiencies Pain was the initial symptom in 41 per cent dysphagia in 11 9 per cent and anorexia in 8 0 per cent When the cardia was involved dysphagia was the first symp tom in 40 per cent Pain was more common when cancer in volved the lesser curvature of the body of the stomach and frequently simulated angina pectoris Anorexia was more fre

(2) A h S g 60 305 33 F brua y 1950

tric ulcers 45 duodenal 6 gastric and duodenal 7 pyloric 5 anastomotic and 1 hypertrophic pyloric stenosis Pyloric stenosis was present in 28 cases In all cases partial gastrectomy with anastomosis of the gastric remnant to the jejunum was performed Three principles were consistently observed (1) In mobilizing the stomach mass ligature of tissues was

POSTOPERATIVE COMPLICATIONS (102 OPERATIONS*)

Com cation	Total	B fo J n 1945	A e J n 1945
Superficial wound infection	15	9	6
Deep wound infection	2	1	1
Atelectasis	11	9	2
Pyrexia of unknown origin cough bronchitis	5	3	2
Burst abdomen	5	4	1†
Bronchopneumonia	2‡	0	2‡
Subhepatic abscess	2	0	2
Lung abscess	2	2	0
Pulmonary embolus	2	2	0
Peritonitis	1‡	0	1‡
Persistent hiccup	1	0	1
Femoral thrombosis	1	1	0
Postoperative gastric bleeding	1§	1	0§
Postoperative melena	1	0	1
Dysentery bloody diarrhea	2	1	1
Penicillin rash	1	0	1
Hydropneumothorax	1‖	0	1‖
Tension pneumothorax and congestive cardiac failure	1‖	0	1‖
Pressure palsy of arm	1	0	1
Empyema	1	1	0
Total complications	58	34	24
Total cases with complications	52 (51%)	34 (61%)	18 (39%)

F fty s x bef 1945 46 aft
†Sk n o ly
‡O e d th h
§Ope t on fo h m h ge (al luded as s bb p t bs ess)
‖F llowed nte co tal blo k

avoided vessels being ligated separately or in small groups (2) Clamps were not used except on edges of gut that were subsequently invaginated (3) Closures and anastomoses were made in two layers with a continuous all coats catgut suture and interrupted seromuscular sutures of fine serum proof silk A Ryle tube placed in position before operation permitted intermittent gastric suction until the fluid balance became positive

The low mortality rate of 2 per cent despite the many poor risk cases the absence of significant gastric retention

x ray in 91 5 per cent of 1 022 patients In 305 patients the incidence of positive diagnosis of 86 9 per cent by x ray study was raised to 96 4 per cent when gastroscopy was used

[The results of this instructive clinical study dovetail with those of large experience in this field in which there is vast room for improvement —Ed]

Fever Common Symptom in Carcinoma of Stomach Doris A Berlin and William B Porter[3] (Med College of Virginia Hosp) studied the histories of 69 patients during 81 admissions Any oral temperature of 99 F or above was considered fever No fever was recorded in 14 81 per cent. In 24 69 per cent fever was ascribable to infection or causes other than neoplasm Fever was classed as of doubtful origin in 12 35 per cent Neoplasm appeared to be the only cause of fever in 49 15 per cent

In the group with fever due to neoplasm temperature elevation was intermittent rather than continuous Rises occurred irregularly and were not sustained During any 24 hour period a typical patient would have several normal readings and perhaps one or two above normal In some cases fever appeared only once or twice during a week There was no predilection for either a nocturnal or a diurnal appearance

Of 11 patients with fever whose stomachs were removed surgically only 3 were reported as having intact mucosa Of 12 patients without fever 2 had ulceration Apparently fever may occur in the absence of ulceration or ulceration may occur in the absence of fever The series did not include sufficient cases of nonmetastatic carcinoma to permit statistical evaluation of the significance of metastatic lesions in production of fever

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THE LIVER PANCREAS AND GALLBLADDER

Observations on Biliary Pancreatic Dynamics in Normal Human Previous studies have usually been conducted on cholycystectomized patients with a T tube in the common duct John D Ryan Henry Doubilet and John H Mulholland[4] (New York Univ) carried out similar studies on an otherwise healthy young man with an external fistula of the right

(3) V gin M Monthly 77 59 65 F bru ry 1950
(4) G t oent logy 13 1 8 J ly 1949

quent with pyloric and prepyloric cancer The greater curva ture of the fundus is the silent region of the stomach and when the cancer site it is seldom responsible for pain or inter ference with passage of food

Stomach cancer may become inoperable before the patient has any symptoms but may be operable when symptoms pre sumably due to cancer have been present for two years When symptoms have been present 18 30 months operative mortal ity is three times as great as when complaints are of shorter duration

There were 155 patients who had gastrointestinal symp toms for more than two years Of these 53 had a history of ulcer like symptoms and 102 gave a vague story of indiges tion In many of the e patients a change in symptoms devel oped which could have been an important clinical clue to the development of stomach carcinoma

There was a palpable epigastric mass in 57 per cent of patients with inoperable gastric cancer and in 42 per cent of those in whom it was operable This does not necessarily indi cate inoperability Aspiration liver biopsy or peritoneoscopy should be used if peritoneal carcinosis or hepatic metastasis is suspected With these aids about 50 per cent of patients with these lesions may be spared the discomforts hazards uselessness and expense of exploratory laparotomy Analysis of physical findings disclosed that 11 per cent of the patients examined had one or more signs such as signal nodes Blum er s shelf ascites jaundice obviously nodular liver or other pelvic implants indicating the inoperable nature of the cancer

Achlorhydria was found in 65 0 per cent of patients with inoperable gastric cancer and in 51 1 per cent of those in whom carcinomas were resectable The incidence of achlor hydria was greater in those with extensive carcinoma or high grade lesions Excessive amounts of free hydrochloric acid were twice as frequent in patients with benign gastric ulcer as in those with gastric cancer and three times as often as in normal adults aged 60 65 No acidity occurred in the same proportion in normal persons of cancer age in patients with gastric cancer and in those with benign gastric ulcer A rela tively high degree of achlorhydria was found in those with polypoid or infiltrating gastric cancers

An unequivocal diagnosis of gastric cancer was made by

hepatic duct the result of a bullet wound Their results paralleled observations on patients with diseased biliary tracts

Morphine sulfate 10 mg was administered subcutaneously followed 15 minutes later by 35 per cent diodrast® solution injected slowly through the fistula by a Foley catheter X rays were taken during this and subsequent injections at 10 minute intervals At the first injection dye outlined the intra and extrahepatic ducts and partially filled the gall



F g 1 0 (l ft) —F lm mad ft p m f ph ct f Odd w p od ed by HCl j ct on to d od n m D od t j t d b ough h tul outl d wh l b l ry ct d p od ed flux p p d ct (w)

F g 121 (ght) —F lm m d n m te ft j ctu f mo ph b w g comp es f t m l po t f mmon d ct (w) d bse f pan eatu d t al zat Not na w g f mp ll f gallbl dde d p t sed p

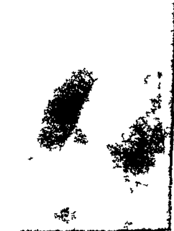
(C rt y f Ry J D et l Gas oe ter l g 13 1 8 J ly 1949

bladder (Fig 116) Thirty minutes after administration of morphine the gallbladder filled completely and the terminal end of the pancreatic duct was visualized (Fig 117) Little dye entered the duodenum Epigastric pain and nausea occurred with each injection of diodrast® and consequent distention of the bile ducts Immediate inhalation of amyl nitrite produced relaxation of the sphincter rendered spastic by morphine allowing the dye to pass rapidly into the intestine (Fig 118) The common duct emptied completely and could not be visualized five minutes later (Fig 119) The gallbladder relaxed









F g 116 (top left) —F lm r d 15 m tes afte dm n t at on of morph e how g b l ry tract o tl d w th diod st and gallbl dd r b g g to f ll No d od a t h s p ed t d d m

F g 117 (t p ght) —W th co tin ed) ct g llbl dd g ad ally filled nd f re d s m diod a t t d od n m Ar w nd t p t l t \ t bull t ly g n b dy f el th tho c rt b (Fo cla ty te m l d of d t this fig re d F gu e 116 we o tl d)

F g 118 (bottom l ft) —Dy di te d d b l y t ct p d r p dly t d o den m afte ph te of Oddi was la ed by myl t t s h l t n

F g 119 (bottom ght) —F lm m de fi m n t fte myl n t ste hal t on B l ducts no l nge s al z d

(Courte y of R J D t al Ga t oe t logy 13 1 8 J ly 1949)

physiologic In one third of the specimens the duct was extra pancreatic in one third intrapancreatic and in one third par tially intrapancreatic An elevated caruncle depressed in 24

Fig 122—Lum n f d od l mmon bile d ct w s n mal was th ck n f w ll Ext d od nal mm b l d ct w ext b p t f 50 per t of ts pan e t c u e P nc t d t w n mal P pill w 15 9 mm. l g d 6 4 mm w d d d al w ll w 12 7 mm. wid A ad B p obe n pa cr d ct u teral ca bet n mmon b l d t C and D w ll f duct rt d. (C rte y f Ste l g J A R G t oenter l 16 821 845 Nov mbe 1949)

per cent of specimens and level with adjacent duodenal mu cosa in 22 per cent marked the termination of the duct A typical dissection is shown in Figure 122

A papilla representing enlargement of the wall of the

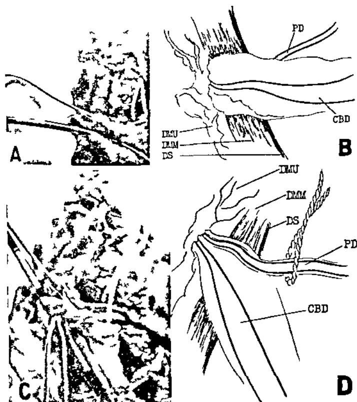
and did not empty While 10 cc of N/10 HCl was rapidly injected into the duodenum through a Rehfuss tube diodrast* was instilled through the biliary fistula Figure 120 shows that the resulting spasm of the sphincter of Oddi forced dye into the pancreatic duct demonstrating the common biliary pancreatic passageway An x ray taken five minutes after subcutaneous injection of morphine sulfate 10 mg showed muscular spasm of the duodenal wall (Fig 121) The lower end of the common duct was compressed and tonus of the gallbladder increased

To demonstrate the effect of a fat meal on intraductal pressure normal saline was perfused into the biliary tract through the fistula and syphoned from the duodenum through a Rehfuss tube A kymographic tracing showed intraductal pressure of 150 mm Two minutes after administration of a 20 cc mixture of olive oil cream and bacon drippings intraductal pressure rose 20 mm Tonic contractions of the gallbladder were noted and a flow of dark concentrated bile appeared in the Rehfuss tube Injection of 10 cc N/10 HCl into the duodenum produced spasm of the sphincter of Oddi Intraductal pressure rose to 190 mm water and then fell rapidly as the effect of the acid decreased Tonus rhythm reappeared when intraductal pressure reached 170 mm At the termination of the experiment intraductal pressure fell gradually to 120 mm These results were comparable with those obtained previously only in animals

Termination of Common Bile Duct Julian A Sterling[5] (Univ of Pennsylvania) studied 80 dissections of the termination of the common bile duct of which 50 were detailed and included microscopy The common bile duct traveled a double S shaped course The proximal curve was extraduodenal and the lumen of the duct in this area averaged 6 3 mm in diameter The distal curve within the duodenal wall was short In the last few centimeters the lumen of the duct tapered like a cone or funnel terminating as a filamentous canal The diameter of the orifice in the duodenal canal averaged 2 mm It would therefore be impossible for a calculus larger than 3 mm in diameter to pass normally through the termination of the duct into the duodenum Likewise passage of large Bakes dilators in surgical manipulation is considered un

(5) Re G t oent ol. 16 8 1 845 N ember 1949

physiologic In one third of the specimens the duct was extra pancreatic in one third intrapancreatic and in one third partially intrapancreatic An elevated caruncle depressed in 24



F g 12 —Lum f t d d l comm n b l d ct w mal w th k f w ll E t d od nal mm b l d ct w t h p t f 50 p t f ts p n t c I t d t w mal e. P p ll w 15 9 mm. long and 6 4 mm. w d d d) w ll w 1 7 mm. w d *A* d *B* pr be pa t c d t t l cath t n common b le d ct. *C* and *D* w ll f d t erted (Co te y f Ste l g J A R G troe t l 16 8 1 845 Novem be 1949)

per cent of specimens and level with adjacent duodenal mucosa in 22 per cent marked the termination of the duct A typical dissection is shown in Figure 122

A papilla representing enlargement of the wall of the

termination of the duct was found due to an increase in the width of the walls caused by presence of a sphincter muscle An ampulla or dilatation of the duct was not observed The papilla averaged 14 1 mm in length and 3 4 mm in thickness In 45 of 46 specimens the mucosa within the papilla formed many folds and reduplications Often these valvules were not fused but were freely movable within the lumen of the common duct so that mucosal fringes extended within the duodenal canal or into a common channel On microscopy muscular and fibrous tissues were found in the valvule In 32 of 50 specimens separate openings for pancreatic and common bile ducts were observed In 18 specimens (36 per cent) presenting a common channel average length of the papilla was 14 4 mm that of the common channel 4 4 mm The common channel was equal in length to the papilla in one specimen In only 1 of 50 specimens did the common channel form outside the duodenal wall Three sets of sphincters were identified in the medial third of the papilla The proximal two surrounded each duct separately the distal one both ducts

The low reported incidence of reflux into the pancreatic duct (just under 16 per cent) as shown on cholangiograms is substantiated by the few specimens found with a long common channel Since the length of the papilla was 1 cm greater than that of the common channel the muscle proximal to the channel (sphincter of Oddi) would prevent interductal reflux Sterling recommends that the term ampulla be deleted from use with reference to any portion of the termination of the common bile duct The expanded distal portion of the duct should be called the papilla Its termination within the duodenum could be called the caruncle or the papilla of Vater

Extrahepatic Biliary System Its Phylogenesis is described by J H Louw[6] (Univ of Cape Town) who has personally dissected the biliary systems of 38 species representing all the vertebrate classes and every placental order

A close relation was found between the phylogenetic development of an animal and the anatomy of its biliary system The primitive biliary system is a complex structure consisting of multiple hepatic ducts and a large gallbladder The biliary systems of more highly specialized species have a simpler structure Accessory hepatic ducts disappear and the

(6) Cl n Proc Cape Town P t G d M A 8 185 2 0 D mber 1949

gallbladder tends to be small Biliary systems of species whose body forms have departed considerably from that of their ancestors are extremely simple No gallbladder is present and there is no compensatory dilatation of the bile ducts

There is a similar relation between the pattern of the gastrointestinal tract and that of the biliary system and both are related to the dietary habits of the animals Species with simple digestive canals have a primitive form of biliary apparatus They are carnivorous and insectivorous Species with minor complexities of the gastrointestinal tract usually possess a gallbladder but no accessory hepatic ducts They are insectivorous and herbivorous Species with the most highly specialized alimentary systems tend to lose the gallbladder They are essentially herbivorous In general the gastrointestinal tract adapts itself more readily to changes in the body form and mode of life of the animal Anatomic complexities of the digestive system precede structural changes in the biliary tract A gallbladder is present even in herbivorous marsupials which possess most complex gastrointestinal tracts but on the other hand no species with a very simple alimentary tract lacks a gallbladder

Functional activity of the biliary system is progressively diminished from the lower to the higher vertebrates This together with progressive loss of form is an indication of the declining needs for a highly efficient bile concentrating mechanism Since bile is necessary for digestion and absorption of fats it is significant that carnivora possess the primitive type of biliary system while herbivora tend to lose the complex biliary system The human biliary system occupies an intermediate position in the phylogenetic development of the biliary system Accessory hepatic ducts represent the arrangement of the primitive biliary system Congenital absence of the gallbladder represents the pattern of biliary system of species which have become highly specialized Anomalies encountered represent different stages in the phylogenetic development of the biliary system

Comparison of Pain Produced Experimentally in Lower Esophagus Common Bile Duct and Upper Small Intestine with Pain Experienced by Patients with Diseases of Biliary Tract and Pancreas Pain localization alone is insufficient to identify clinically the visceral structure involved William P

Chapman Rudolfo Herrera and Chester M Jones[7] (Harvard Univ) compared experimentally produced and clinical pain to determine whether pain arising from bile ducts and duo denum may have an identical area of localized reference in any given patient Of nine patients studied seven had biliary tract disease and two pancreatitis Experimentally pain was produced by distending the common duct cardiac end of the esophagus and duodenum or upper jejunum The person was asked (1) to report any sensation (2) to outline the area

TABLE 1 —COMPARISON OF PAIN EXPERIMENTALLY PRODUCED IN UPPER ABDOMINAL VISCERA

V cera S mul ted	Total Cases	Cases with I entic l Pain	C s s w th Diff e t P n
Esophagus upper small intestine and common duct	9	3	6
Esophagus and upper small intestine	9	3	6
Esophagus and common duct	9	5	4
Upper small intestine and common duct	9	7	2†
Duodenum and jejunum	5	5	0

Ind t gu h ble as t q al ty loc t on t ty and ad t
†P w tl e s m pt f a d ff n e in ad t

TABLE 2 —PAIN EXPERIMENTALLY PRODUCED REPRODUCING CLINICAL PAIN OF BILIARY TRACT AND PANCREATIC ORIGIN

Visc ra Stimulate	T t l C s	Cas s with Ide c l Pain	C s w h D P
Common duct	9	7	2†
Upper small intestine	9	7	2†
Esophagus	9	4	5

S m n q l ty locat o d d t on
†Pa n w the me pt for a d ffe e ce n d t on

of sensation (3) to describe quality intensity depth and ra diation of sensation and (4) to compare the sensation with his clinical pain In each viscus studied the test was repeated at least three times

In the same patient similarities were found among pains induced by distention of different viscera in terms of location radiation quality and intensity However the amount of dis tention necessary to elicit pain of comparable intensity varied among patients Pain from distention of the common duct and upper small intestine was the same in seven patients and dif ferent in two When the lower esophagus was included in the comparison distention produced identical pain in only three patients Results are summarized in Table 1 Results of com

(7) S g Gy ec & Ob t 89 573 582 N ember 1949

parison of clinical pain with that induced experimentally are given in Table 2 In seven patients clinical pain was reproduced by distention of the common duct and of upper small intestine In four patients distention of the lower end of the esophagus produced pain similar to their clinical pain in the other five the chief difference was one of location

The striking similarity of pain induced from stimulation of (1) the common duct and upper small intestine and of (2) experimentally induced pain to that of biliary tract disease and pancreatitis emphasizes the difficulty in distinguishing between disturbances of these structures on the basis of pain symptoms alone *Possibly the similarity may be due to the* viscera having a common sensory supply the great splanchnic and lower thoracic sympathetic nerves

Significance of Bilirubin Partition in Hepatobiliary Diseases Because the diagnostic significance of partition of serum bilirubin into direct and indirect fractions in jaundice exclusive of the hemolytic form is not clearly established Fenton Schaffner Hans Popper (Northwestern Univ) and Frederick Steigmann[8] (Univ of Illinois) investigated this question in 279 jaundiced patients with verified diagnoses In addition 31 normal adults were used as controls

In evaluating the diagnostic value of the van den Bergh reaction initial values only were considered (Table 1) Patients with extrahepatic biliary obstruction had the highest concentration of both total and prompt reacting bilirubin whereas those with cirrhosis had the lowest values The ratios of prompt reacting to total bilirubin were similar in cirrhosis and infectious hepatitis on the one hand and in toxic hepatitis and obstructive jaundice on the other The significance of the difference between the means for prompt reacting and total bilirubin and prompt total bilirubin ratio was statistically expressed by t values (Table 2) Some of the differences in the bilirubin concentrations were statistically significant e g the difference in total bilirubin between cirrhosis and other forms of jaundice and in prompt reacting bilirubin between biliary obstruction and cirrhosis or infectious hepatitis There was no significant difference between biliary obstruction and toxic hepatitis or *between toxic and infectious hepatitis* The only significant difference in prompt total bilirubin ratio was

(8) Am J M Sc 219 307 313 March 1950

found between extrahepatic biliary obstruction and cirrhosis

Differences in total and prompt reacting bilirubin are of little differential diagnostic value Only in cirrhosis are both less elevated on the average than in the other conditions They reflect the stage rather than the etiology of jaundice Elevation of the prompt reacting fraction in subsiding jaundice indicates persistence of the disease

The most significant change in serum bilirubin fractions between normal serum and serum from jaundiced patients

TABLE 1—MEAN PROMPT REACTING AND TOTAL SERUM BILIRUBIN AND PROMPT TOTAL BILIRUBIN RATIOS IN 279 JAUNDICED PATIENTS AND 31 CONTROLS*

Diagnosis	No of Patients	Prompt Reacting Mg/100 Cc	Total Mg/100 Cc	Prompt Total Ratio %
Normal	31	0.15	0.51	29.41
Cirrhosis	114	4.34	9.90	38.64
Infectious hepatitis	44	5.32	14.58	38.96
Toxic hepatitis	37	6.86	15.43	43.48
Extrahepatic biliary obstruction	84	8.16	18.72	43.45

* Initial determinations only

TABLE 2—T VALUES FOR DIFFERENCES IN MEANS OF PROMPT REACTING AND TOTAL SERUM BILIRUBIN AND PROMPT TOTAL BILIRUBIN RATIO BETWEEN VARIOUS ETIOLOGIC FORMS OF JAUNDICE*

	Prompt Reacting	Total	Prompt Total Ratio
Biliary obstruction—cirrhosis	4.67	5.60	2.69
Biliary obstruction—infectious hepatitis	3.20	1.96	1.73
Biliary obstruction—toxic hepatitis	0.96	1.15	0.01
Infectious hepatitis—cirrhosis	1.33	2.88	0.12
Toxic hepatitis—cirrhosis	2.00	2.06	1.79
Toxic hepatitis—infectious hepatitis	1.18	0.28	1.40

* A t value above 2.00 indicates a significant difference

exclusive of those with hemolytic jaundice is that the ratio of prompt reacting to total bilirubin is increased As jaundice becomes very deep the ratio tends to decrease although not to the level of serum from nonjaundiced patients These changes occur in both parenchymal and obstructive jaundice Differences in prompt total bilirubin ratio are therefore related to the level of total bilirubin rather than to the disease The amount of prompt reacting serum bilirubin depends on the degree of jaundice As jaundice develops the prompt reacting fraction increases more than the indirect When jaundice is established the rise of both fractions is fairly parallel

When bilirubinemia exceeds 40 mg /100 cc the increase of the indirect fraction is greater than that of the prompt reacting one

Comparison of the histologic picture of 153 liver biopsy specimens revealed no relation between presence or absence of jaundice and degree of liver cell damage There was a slight *significant correlation between presence of liver cell damage* and absolute values of prompt reacting and total bilirubin

These observations support the concept that bilirubin is changed from the indirect to the prompt reacting form in the Kupffer cells and is transmitted to liver cells for excretion The small amounts of prompt reacting bilirubin normally present in the blood are present because they have not been taken up by the liver cells In parenchymal jaundice liver cells are unable to accept all of the bilirubin and in obstructive jaundice they are unable to excrete it The result is a return of prompt reacting bilirubin to the blood and accumulation of bilirubin in Kupffer cells This accumulation impairs bilirubin uptake and results in subsequent indirect bilirubin increases

Limitations and Merits of Single Serum Sample Analysis in Differential Diagnosis of Jaundice are considered by F W Hoffbauer E D Rames and J K Meinert[9] (Univ of Minnesota) The biochemical procedures used on single serum samples *from 77 patients with extrahepatic biliary obstruction* and 70 with parenchymal liver disease are listed in Table 1 The values presented in Table 2 indicate the anticipated re

TABLE 1—BIOCHEMICAL PROCEDURES USED

P ce u	M h	N m V u
1 Serum bilirubin	Malloy & Evelyn as modified by Ducci & Watson	1 (prompt direct) 0.2 mg /100 cc (total direct + indirect) 1 0 mg /100 cc
2 Cephalin cholesterol flocculation	Hanger	A reading greater than 1 + at 24 hr may be considered abnormal
3 Thymol turbidity	Maclagan	0 4 units
4 *Serum cholesterol* (total)	Schoenheimer & Sperry	180 220 mg /100 cc
5 Serum cholesterol (esterified fraction)	Schoenheimer & Sperry	50 65% of total
6 Alkaline phosphatase	Bodansky	1 4 units/100 cc

(9) J Lab & Cl M d 34 1259 1278 S pt mbe 1949

sults assuming that the procedures would always yield results of differential diagnostic value Instances in which the actual results failed to conform with those listed in Table 2 are tabulated in Table 3

Certain characteristic biochemical responses occur fairly uniformly as a result of hepatic disease and bile duct obstruction Most patients with extrahepatic bile duct obstruction

TABLE 2—ANTICIPATED RESULTS IN BIOCHEMICAL TESTS USED BY AUTHORS

Type of Liver Disease	Cephalin Cholesterol (24 Hr Reading)	Thymol Turbidity (Maclagan)	Total Serum Cholesterol	Cholesterol Ester	Alk Phosphatase (Bodansky)
Extrahepatic obstruction	1+ or below	0 4 units	Above 225 mg /100 cc.	Above 50%	Above 10 units
Parenchymal liver disease	Above 1+	Above 4 units	Below 225 mg /100 cc	Below 50%	Below 10 units

TABLE 3—INSTANCES IN WHICH ACTUAL RESULTS FAILED TO CONFORM WITH ANTICIPATED RESULTS

Disease	Cases	Cephalin Cholesterol	Thymol Turbidity	Serum Cholesterol	Cholesterol Ester	Alkaline Phosphatase
Carcinoma	28	2	4	5	21	3
Common duct stone	39	2	1	12	11	12
Common duct stricture	10	0	1	3	2	1
Total	77	4	6	20	34	16
Cirrhosis	26	9	9	9	16	13
Hepatitis	31	5	6	11	10	8
Miscellaneous hepatic disease	13	10	9	2	6	4
Total	70	24	24	22	32	26

show elevated cholesterol and alkaline phosphatase levels but respond normally to thymol turbidity and cephalin cholesterol flocculation tests Many patients with jaundice due to diffuse liver disease exhibit biochemical changes of an opposite nature giving such tests a differential diagnostic value However, some patients with parenchymal liver disease show cer

tain changes that closely parallel those seen in extrahepatic obstruction

This limitation of the use of the liver function test reflects a basic pathologic phenomenon Diffuse liver damage exist ing in hepatitis and cirrhosis may manifest itself with varying emphasis on hepatocellular or cholangiolar functional impair ment The former is the classic type and resultant biochemical changes are quite characteristic and readily recognizable When the latter predominates the results of the tests may prove misleading from a differential diagnostic standpoint

[One interesting aspect of th s contribution is a di cu sion of the minimum yet presumably adequate group of liver function tests proposed in the past five years by different American investigators for differential diagnosis of jaundice As in the search for the Northw est Pa sage certain difficulties are always being encountered —Ed]

Quantitative Correlation of Morphologic Liver Changes and Clinical Tests was studied by Hans Popper Frederick Steigmann and Paul B Szanto[1] (Chicago) to determine (1) the statistical correlation between abnormalities in results of liver function tests and liver cell changes (2) which tests show the best correlation (3) if the number of tests with ab normal results is related to the degree of liver cell changes (4) if correlation between severity of liver cell damage and degree of functional impairment is related to the specific liver disease present and (5) which tests may be used as screen ing tests for presence of hepatic damage

Of 257 biopsy specimens 196 were obtained by Turkel needle aspiration and 61 by excision from patients with infec tious and toxic hepatitis cirrhosis with and without jaundice extrahepatic biliary obstruction with and without infection and various gastrointestinal disorders for which laparotomy was performed

Hepatic tests were done at the time of or within two days before or after biopsy and were graded in abnormality from 0 to 3+ Liver cell changes were graded 0 to 3+ progressing from uniform appearance of cells and nuclei (0) to moderate variations with uniform cytoplasm (1) moderate irregular ity of cells with nuclear abnormalities and/or changes in cyto plasm (2) and striking abnormalities (3)

The degree of structural liver cell damages of biopsy tis sue was statistically correlated with the degree of abnormality

(1) Am. J Cl P th 19 710 724 A g t 1949

in results of the series of liver function tests even though in individual cases no correlation existed Such correlation indicates only an association and does not establish that liver cell damage causes the test results Results of tests for total serum protein and cholesterol fecal urobilinogen nonprotein nitrogen prothrombin time and sedimentation rate had no significant association with degree of liver damage Urinary urobilinogen and alkaline phosphatase tests showed qualitative but not quantitative correlation with hepatic damage for biliary obstruction reduces urinary urobilinogen and elevates the alkaline phosphatase values independent of liver damage The degree of liver damage was significantly correlated with the serum bilirubin albumin globulin and flocculation tests Association with a decrease in albumin is explained by formation of albumin in liver cells Globulin increase is due to the mesenchymal reaction in many forms of hepatocellular injury except extrahepatic biliary obstruction without infection This accounts for the close correlation of cephalin flocculation and thymol turbidity with the degree of liver damage since both tests depend on elevation of globulins and decrease in albumin If secondary infection complicates extrahepatic biliary obstruction however these tests become positive

The greater the severity of liver damage the greater the number of positive liver tests independent of the physiologic basis of the test For screening purposes the cephalin flocculation and urinary urobilinogen tests are the most helpful since positive results indicate liver damage whereas negative results do not exclude it in presence of biliary obstruction

Differential Diagnosis of Jaundice Bernardo Sepulveda Horacio Jinich and Eduardo Barroso[2] review 125 cases studied between January 1947 and September 1948 There were 66 females and 59 males mostly adults For the purposes of this study only patients were classified as having one of three types of jaundice (1) prehepatic hemolytic or non hemolytic (2) intrahepatic parenchymal or cholangitic both acute and chronic (3) posthepatic benign or malignant without or with secondary hepatic lesion Diagnosis was confirmed by autopsy in 60 cases by liver biopsy in 33 and by operation in 14 (85 6 per cent altogether) in the other 18 the clinical picture and laboratory data did not leave any doubt as to diag

( ) Rev e t g c on cl 1 169 189 J ly 1949

nosis In all patients a clinical history was taken and routine laboratory examinations were made liver function tests were repeated every 10 days in acute and every 20 days in chronic cases Special studies were made when indicated

Diagnosis of prehepatic jaundice generally was not difficult In diagnosis of intra or posthepatic jaundice there are useful and useless clinical laboratory and roentgenologic data Useful data are those which occur frequently or exclusively *in one type of jaundice and rarely or not at all in* another type The value of individual data must always be considered in connection with the entire picture Despite recent development of laboratory technics a good clinical history continues to serve as foundation for diagnosis With clinical data alone diagnosis was made in 70 per cent of these cases Roentgenologic and laboratory examinations are valuable aids when their results are judiciously interpreted 25 per cent of these cases were diagnosed with their use When these methods do not establish diagnosis liver biopsy may identify cholangitic or posthepatic jaundice with secondary liver lesion

In cholangitic jaundice the symptomatic picture and some laboratory data are similar to those of benign posthepatic jaundice but the anatomicopathologic lesions predominate in the intrahepatic biliary canaliculi while the liver cells remain relatively intact There is no obstruction of the extrahepatic biliary passages This variety is rare It occurred in only 3 2 per cent of the 125 cases In practice it is found that these patients are operated on for obstruction of extrahepatic ducts When cholangitic jaundice becomes chronic it causes cholangitic cirrhosis which is similar to Hanot s cirrhosis

[Herewith is a glimpse into the attitude some of our friends below the border have toward the problem of jaundice from the diagnostic standpoint —Ed]

Needle Biopsy of Liver Experiences in Differential Diagnosis of Jaundice are reported by F G Weisbrod L Schiff E A Gall F P Cleveland and J R Berman[3] (Univ of Cincinnati) *From 157 patients with jaundice 181* adequate liver biopsies were obtained Figure 123 shows that diagnosis based on biopsy was much more reliable than that based on the combined results of cephalin flocculation thymol turbidity and

(3) G t ter l gy 14 56 72 J a y 1950

serum alkaline phosphatase determinations in the various forms of jaundice studied Errors in differentiating virus hepatitis from obstructive jaundice on the basis of needle biopsy are more likely to occur late in the course of virus hepatitis or in milder cases Morphologic changes in the first two weeks of obstructive jaundice may be wrongly ascribed

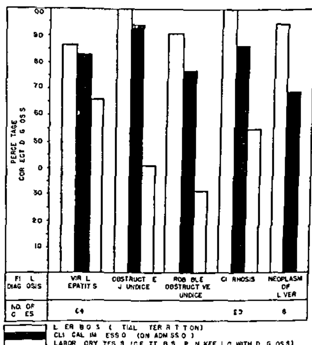


Fig 123—Accu cy of t l d g o s of ca se of j d e m d by l er b psy cl al ex m t on d l bo to y t ts (C t y of W b od F G t l Ga troent ol gy 14 56-72 Jan ry 1950)

to virus hepatitis Diagnostic efficiency improves as the person performing the biopsies and the pathologist interpreting them become more experienced

[The conclusions of the authors of this instructive article are in striking agreement with those of Krarup (Acta med. Scandinav vol 136 supp 234 1949) whose authoritative and illuminating review in English I heartily recommend to all readers interested in this field.—Ed.]

↓ The following articles by Ricketts Palmer and their associates are two of an instructive series dealing with studies of serum proteins in various types of hepatic disease by means of the reliable Tiselius apparatus Their findings are largely in agreement with those of other investi

gators notably those of Whitman Rossmiller and Lewis in untreated cases of portal cirrhosis (J Lab & Clin Med 35 167 180 February 1950) The beneficent results of modern methods of treatment are confirmed by their observations —Ed

Serum Proteins in Portal Cirrhosis under Medical Management Electrophoretic Studies *Kenneth Sterling William* E Ricketts Joseph B Kirsner and Walter L Palmer[4] (Univ of Chicago) carried out such studies on five patients with hepatic insufficiency and ascites during the course of medical management for periods up to 10 months and on five who had been severely ill with hepatic insufficiency but had clinically recovered with treatment and remained asymptomatic for over 2 years All patients were chronic alcoholics with proved portal cirrhosis

The patients in the first group initially had marked diminution of albumin fractions and elevation of gamma globulin fractions with somewhat less elevation of beta globulins During medical treatment serum proteins progressively approached normal coinciding with clinical improvement However in two patients when clinical recovery was considered complete electrophoretic determinations still disclosed appreciable abnormalities in serum protein composition Determinations in the second group showed that the serum proteins may eventually become normal or nearly so in cases of long term recovery under medical management

Infusions of plasma were followed by increases in albumin beta and gamma globulin fractions and total proteins The immediate effects of administration of salt poor concentrated human albumin were striking elevation of albumin and depression of globulin fractions presumably due to dilution Shortly thereafter some decline of albumin and rise of gamma globulin and other globulin fractions occurred These changes may have resulted from decreased plasma volume as albumin left the circulation and subsequent concentration of globulin

Comparison of the alteration of serum proteins with results of various tests of hepatic function performed simultaneously failed to reveal any direct correlation

Electrophoretic Studies of Serum Proteins in Portal Cirrhosis William E Ricketts Kenneth Sterling Joseph B Kirsner and Walter L Palmer[5] (Univ of Chicago) investigated

(4) J Cl I t g t 28 1236 1245 Septembe 1949
(5) G t oe t l gy 13 05 211 S pt mb 1949

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